Exhibit 1

RECEIVED
CENTRAL FAX CENTER

NOV 16 2007

PTO/SB/26 (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 01-40326-US-C

In re Application of: Gans et al.

Application No.: 10/825,977

11/19/2007 PCHUNP 00000001 10825977
01 FC:2814 65.00 OP

Filed: April 16, 2004

For: Compositions and Methods for Enhancing Corticosteroid Delivery

The owner*, Medicis Pharmaceutical Corporation, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term **prior patent** No. 6,765,001 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 44,677

Signature — Date: 11/16/07

Maryellen Feehery Hank
Typed or printed name

215-241-7988
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Exhibit 2

RECEIVED
CENTRAL FAX CENTER
NOV 16 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gans, et al

Serial No. 10/037,360

Filed: December 21, 2001

Art Unit: 1617

Examiner: Mojdeh Bahar

Attorney Docket No.: 01-40326-US

COMPOSITIONS AND METHODS FOR ENHANCING CORTICOSTERIOD DELIVERY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION

1. I, Dr. Eugene H. Gans, am a named inventor of the above-referenced patent application. I received a Bachelor of Science (B.S.) in 1951 from Columbia University New York, New York; a Master of Science (M.S.) in 1953 from Columbia University New York, New York; a Doctor of Philosophy (Ph.D.) in 1956 from the University of Wisconsin Madison, Wisconsin. Starting in 1956 and continuing to the present, I have been involved in the development and testing of dermatologic drug delivery systems. I am presently a Senior Advisor to Medicis Pharmaceutical Corp. and am involved in the development and licensing of cosmetic and drug delivery systems. For several years, beginning in 1989, I had been a member of the AAPS/FDA/NIH/Academia/Industry Planning Committee to Establish Criteria for Assessing the Absorption of Active Agents & Drugs Into and Within the Skin.

2. When applied to the skin, topical corticosteroids produce a localized skin-blanching response, caused by constriction of the superficial blood vessel of the skin. (*See* Stoughton RB. Vasoconstrictor assay-specific applications. In: Maibach HI, Surber C. eds.

Topical Corticosteroids. Basel:Karger; 1992:42-53; McKenzie AW, Stoughton RB. Method for Comparing Percutaneous Absorption of Steroids. *Arch Dermatol*. 1962; 86:608-610.) (attached as Exhibit A). The degree of skin blanching, which can be assessed by careful visual scoring, serves as a measure of the inherent potency of the drug and its capacity to diffuse through the stratum corneum, and is known by one skilled in this field.

3. The vasoconstrictor assay is the most widely used technique to assess the potency of topical corticosteroid compositions. It correlates well with the clinical efficacy of corticosteriod formulations. Workers in this field use it to identify and optimize new formulations for clinical development.

4. The U.S. FDA requires the submission of *in vivo* bioequivalence in abbreviated new drug applications (ANDA) for topical corticosteriod compositions. (21 C.F.R. § 320) of various potency groups. Guidance from the FDA, effective June 2, 1995, recommends that vasoconstrictor assays be used for this purpose. The FDA publication further states that "[m]ost of the currently available generic topical corticosteroids have been approved on the basis of [a vasoconstrictor bioassay]." (See Guidance for Industry, Center for Drug Evaluation and Research, Food and Drug Administration, page 3 (1997), *available at* <http://www.fda.gov/cder/guidance/old098fn.pdf>) (attached as Exhibit B).

5. The relative potency of topically applied corticosteroids are ranked by class, based on vasoconstrictor testing, with Class I being the most potent and Class VI being the least potent. (See Anti-inflammatory Agents, American Hospital Pharmacy Service (AHFS) Drug Information Manual, page 3403 (2003) (the "AHFS Manual")) (attached as Exhibit C).

6. As is known to persons skilled in this field, activity of a topical corticosteriod preparation may vary greatly and unpredictably based, in part, on the vehicle or

formulation. The AHFS Manual further points out that "*activity may vary considerably depending upon the vehicle*." Id. (Italics in original). As shown in the AHFS Manual, the topical coricosteroid betamethasone dipropionate exists in each of Class III, II and I, even though the listed concentration of betamethasone dipropionate in each preparation in the same 0.05%. Id.

7. The anti-inflammatory activity of topical corticosteroid compositions is based upon differences in vasoconstrictor test scores. (AHFS Manual, page 3403). For example, Class I topical corticosteroid compositions often exhibit a vasoconstrictor score of 80 or above, while Class II topical corticosteroid compositions often exhibit a vasoconstrictor score of less than 80. Further, the more potent Class 1 topical corticosteroid compositions are restricted in their use because of the clinical potential to induce adrenal cortex suppression. Thus, the clinical and physiological differences between, for example, Class I and Class II topical corticosteroid compositions, is also manifested by the different restrictions that FDA places on their use.

8. The FDA requires the submission of vasoconstrictor scores in NDA, (See Guidance for Industry, *supra*) and, very importantly, one must show that the vasoconstrictor score is comparable in magnitude to the vasoconstrictor test score produced by an already FDA approved, topical vasoconstrictor in the desired class. For example, in a new drug application requesting approval of a product according to the present invention as a Class I - topical corticosteroid composition, it must produce a vasoconstrictor score comparable to an already FDA approved vasoconstrictor, for instance, Clobetasol®. In these tests, the score for Clobetasol® was above 80, and thus, scores below 80 are not acceptable to FDA as demonstrating Class I activity, as epitomized by Clobetasol®. More specifically, the commercially available topical fluocinonide composition Lidex®, which has a vasoconstrictor score of less than 80, is currently classified as a Class II steroid.

9. Thus, the difference in vasoconstrictor scores of 71 and 85 for fluocinonide represents real, clinical and physiological differences by placing topical fluocinonide in specified vehicles producing these scores into separate classes. As illustrated in the present invention, the average of summed vasoconstrictor score of 85 was the result of a ratio of penetration enhancers, to (penetration enhancers and solvents and emulsifiers) of at least about 0.90 versus an average of summed vasoconstrictor scores of 71 for of a ratio of penetration enhancers, to (penetration enhancers and solvents and emulsifiers) of at least about 0.80 (see Table 2, paragraph 26 of the present application). The effect of altering of the ratio of penetration enhancers, to (penetration enhancers and solvents and emulsifiers) which provides for the rise in vasoconstrictor scores from 71 to 85, with the associated rise from Class II to Class I, is an entirely unexpected result.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully Submitted,

Dated: 2/23/04

Dr. Eugene H. Gans

EXHIBIT A

Method for Comparing Percutaneous Absorption of Steroids

A. W. McKENZIE, M.R.C.P.
LONDON
AND
R. B. STOUGHTON, M.D.
CLEVELAND

A simple method for assessing the percutaneous absorption of steroid preparations is suggested.

Using vasoconstriction as an index of absorption, occlusion of the skin surface with Saran Wrap results in a 100-fold difference in absorption over simple topical application.

Garb [1] was the first to use thin plastic films in dermatological therapy, and subsequently other workers have testified to the usefulness of plastic film applied over a variety of topical preparations. Scholtz [2] reported good results in recalcitrant psoriasis using fluocinolone cream under Saran Wrap after preliminary abrasion of the lesions with Brasivol. Sulzberger and Witten [3] used triamcinolone acetonide ointment under plastic films and in obstinate psoriasis achieved results which equalled those obtained with intralesional injection of steroid. The latter authors attributed the enhanced activity of steroid applied under a plastic film to better contact between ointment and skin, more accurate localization of the ointment, and increased percutaneous absorption as a result of epidermal maceration and increased skin temperature.

Our own good therapeutic results with this method of treatment led us to attempt a quantitative comparison of the percutaneous absorption of steroid hormones applied to normal skin with and without occlusion. The clinical observation that treatment with topical steroid and Saran Wrap first produced pallor of the lesion and of the surrounding normal skin suggested that vasoconstriction might be used as an index of the percutaneous absorption of the steroid. We could find no report in the literature of the vasoconstrictor activity of steroids when applied to healthy unbroken skin, although Ashton and Cook [4] observed vasoconstriction in super-

Fellow in Dermatology (Dr. McKenzie), Western Reserve University; Present address: St. Thomas' Hospital, London S.E.1, England; Director of Dermatology (Dr. Stoughton), Western Reserve University.

Supported by a grant from the Department of Health, Education, and Welfare.

Fig. 1.—Metal guard and Saran Wrap in position.

ficial corneal vascularization treated with subconjunctival steroids, and Hollander et al.[3] reported that intra-articular steroids produced blanching of the engorged synovial membrane in rheumatoid arthritis. It would seem reasonable to postulate that this vasoconstriction is in part responsible for the anti-inflammatory activity of these compounds. Our experiments so far (to be published in full at a later date) indicate that although wide differences exist depending upon the particular steroid and base used, the vasoconstriction produced in normal skin may be useful as an indicator of the percutaneous absorption of steroid preparations.

Method

To assess the effect of Saran Wrap on absorption, 3 steroid preparations were used, dexamethasone alcohol,* triamcinolone acetonide,† and fluocinolone acetonide.‡ Solutions or suspensions of these compounds were prepared in 95% alcohol in dilutions ranging from 1:100 to 1:5,000,000. Using human volunteers, 0.02 ml. of the various dilutions were applied from a dropping pipette on the flexor aspects of both forearms, lightly spread over an area of 1 inch diameter and allowed to dry. To 1 arm was strapped a perforated aluminum guard covering the site of application of the preparations, and the other was wrapped in one layer of Saran Wrap (Dow Chemical Co.) and covered with 2 thicknesses of Tubegauz (Scholl Mfg. Co., N.Y.) (Fig. 1). The areas were left undisturbed for 16 hours, and any sites of vasoconstriction were then noted. Three patterns of vasoconstriction were seen: (1) perifollicular (2) pallor at periphery of application site (3) diffusely in the circular area of application. The degree of vasoconstriction varied with test subject and compounds used, but no attempt was made to grade its intensity. Vasoconstriction was expressed as "present" or "absent." Figure 2 demonstrates the vasoconstriction produced by fluocinolone acetonide.

Fig. 2.—Vasoconstriction produced by dilutions of fluocinolone acetonide. Upper arm, Saran Wrap; lower arm, metal guard.

Results

Table 1 indicates the number of subjects reacting to the various dilutions under Saran

* Supplied by Merck Sharp & Dohme Research Laboratory, Pa.

† Supplied by E. R. Squibb & Sons, N.Y.

‡ Supplied by Syntex Laboratories Inc., N.Y.

TABLE 1.—*Subjects Showing Vasoconstriction at Serial Dilutions*

Steroid	No. of Subjects	Saran						Guard			
		1:100	1:1,000	1:10,000	1:100,000	1:1,000,000	1:10,000,000	1:100	1:1,000	1:10,000	1:100,000	1:1,000,000
Dexamethasone	13	13	13	11	5	0	0	9	1	0	0	0
Triamcinolone acetonide	11	11	11	11	10	7	0	11	11	8	0	0
Fluocinolone acetonide	8	8	8	8	8	6	2	8	8	7	0	0

Wrap, as compared with various dilutions under the perforated guard.

Table 2 shows the average "end-point" of reaction of these compounds under Saran Wrap and the metal guard. It can be seen that with occlusion this end-point differs by a factor of 100 over simple application of the compound.

TABLE 2.—*Average "End-Point" of Vasoconstriction*

Compound	Saran	Guard	Absorption Factor
Dexamethasone	1:10,000	1:100	× 100
Triamcinolone acetonide	1:1,000,000	1:10,000	× 100
Fluocinolone acetonide	1:1,000,000	1:10,000	× 100

Comment

These experiments appear to explain the efficiency of this method of topical therapy in terms of increased absorption. After occlusion of an arm with Saran Wrap for several hours there is obvious hydration of keratin; the hydration of keratin decreases and returns to normal in approximately 30 minutes when evaporation is allowed to proceed. Hydration of the skin has previously been shown to increase the percutaneous absorption of various substances (Rothman [6] and Cronin and Stoughton [7]). Temperature increase may also play a part since thermometers placed under the Saran Wrap for 16 hours showed that the occluded skin temperature equaled internal body temperature.

R. B. Stoughton, M.D., Director of Dermatology, Western Reserve University, Cleveland, Ohio.

REFERENCES

1. Garb, J.: Nevus Verrucosus Unilateralis Cured with Podophyllin Ointment, Arch. Derm. 81: 606, 1960.

2. Scholtz, J. R.: Topical Therapy of Psoriasis with Fluocinolone Acetonide, Arch. Derm. 84:1029, 1961.

3. Sulzberger, M. B., and Witten, V. H.: Thin Pliable Plastic Films in Topical Dermatological Therapy, Arch. Derm. 84:1027, 1961.

4. Ashton, N., and Cook, C.: In Vivo Observations of the Effects of Cortisone upon the Blood Vessels in Rabbit Ear Chambers, Brit. J. Exp. Path. 33:445, 1952.

5. Hollander, J. L.; Stoner, E. K.; Brown, E. M., Jr., and De Moor, P.: The Use of Intra-Articular Temperature Measurement in the Evaluation of Antiarthritic Agents, Ann. Rheum. Dis. 9:401, 1950.

6. Rothman, S.: Physiology and Biochemistry of the Skin, Chicago, University of Chicago Press, 1954, p. 52.

7. Cronin, E., and Stoughton, R. B.: in Brit. J. Derm., to be published.

EXHIBIT B

CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

GUIDANCE*
TOPICAL DERMATOLOGIC CORTICOSTEROIDS: *IN VIVO* BIOEQUIVALENCE

Issue Date: 2 June 1995

I. INTRODUCTION

This *Guidance* provides recommendations to pharmaceutical sponsors on methods to document *in vivo* bioequivalence of topical dermatologic corticosteroids, hereinafter referred to as topical corticosteroids. The *Guidance* becomes effective 2 June 1995. Any investigations initiated after that date should generally conform to the recommendations of the *Guidance*. The *Guidance* utilizes a pharmacodynamic approach, based on an update of the Stoughton-McKenzie vasoconstrictor bioassay, to assess bioequivalence of topical corticosteroids. The method utilizes a duration of exposure (dose duration) approach to control the dose of topical corticosteroid that is delivered. The proposed methodology includes a pilot dose duration-response study to determine the appropriate dose duration for use in the pivotal study, followed by the pivotal *in vivo* bioequivalence study incorporating replicate design and documentation of acceptable individual subject dose duration-response. As with all bioanalytical methods, this pharmacodynamic bioassay will require careful validation on the part of pharmaceutical sponsors.

Potent topical corticosteroid products may suppress the hypothalamic-pituitary-adrenal (HPA) axis. In the past, when *in vivo* bioequivalence of such products was documented using the single time point Stoughton-McKenzie study design, the Office of Generic Drugs (OGD) required an HPA axis suppression test when test and reference formulations were significantly different. Products documented to be bioequivalent using this *Guidance* will not be required to submit HPA axis suppression test data.

The 1 July 1992 *Interim Guidance, Topical Corticosteroids: In Vivo Bioequivalence and In Vitro Release Methods*[1] included dermatopharmacokinetic (skin stripping) studies and *in vitro* release studies. The agency currently has insufficient data to recommend skin stripping methods to document bioequivalence of topical corticosteroids. However, this methodology for documentation of bioequivalence may be used if appropriate validation data are provided. At the present time, OGD will not require *in vitro* release data to support approval of ANDA's for topical corticosteroids. Following future recommendations of the Scale-Up and Post-Approval Changes for Semisolids (SUPAC-SS) Working Group, OGD may recommend the submission of *in vitro* release

---

* This statement has been prepared by the Division of Bioequivalence in the Office of Generic Drugs, with the participation of the Division of Topical Drug Products in the Office of Drug Evaluation II and the Division of Biometrics in the Office of Epidemiology and Biostatistics. It is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the two reviewing divisions at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research. For information about this guidance, contact the Division of Bioequivalence, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-594-2290; Fax: 301-594-0181).

data to support waiver of *in vivo* bioequivalence of the lower strength(s) of topical corticosteroid products, scale-up of production batches, and approval of formulation, process, and site changes in the absence of *in vivo* data. Future use of these data as a quality control tool is also envisioned.

The *Guidance* has been prepared by staff of the Division of Bioequivalence (HFD-650), with the participation of staff of the Division of Topical Drug Products (HFD-540) and the Division of Biometrics (HFD-710). It is a general guidance intended to apply to topical corticosteroids of all potency groups. Because dose duration-response characteristics may vary with the particular drug of interest, as well as with study conditions, the *Guidance* encourages the performance of a pilot study to define appropriate parameters for the pivotal study. Staff members of HFD-650 are available to work with pharmaceutical sponsors in the design of specific studies to meet the recommendations of the *Guidance*.

II. BACKGROUND

The determination of bioequivalence of two solid oral dosage forms generally rests on a comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single or multiple doses of each drug product to healthy volunteers. In the absence of this methodology, the Food and Drug Administration may, through provisions of the Food, Drug and Cosmetic Act and implementing regulations (21 CFR § 320), rely on other *in vivo* and *in vitro* methods to assess bioequivalence. In descending order of preference within the Office of Generic Drugs, these methods include: 1) pharmacodynamic effect studies; 2) clinical trials, 3) *in vivo* animal studies; and 4) *in vitro* studies. Although the methods in the latter two categories are acceptable from a statutory/regulatory standpoint, the Division of Bioequivalence in OGD historically has relied only on *in vivo* pharmacodynamic or clinical studies to assess bioequivalence of drug products that do not produce measurable concentrations of drug or metabolite in an accessible biological fluid. Clinical trials generally require large numbers of subjects and often lack sensitivity. In contrast, pharmacodynamic effect studies offer the possibility of developing acceptable bioequivalence data in a relatively small number of subjects.

For many years, the Division of Bioequivalence has relied on pharmacodynamic effect methodology to approve generic topical corticosteroid drug products. The approach is based on the property of corticosteroids to produce blanching or vasoconstriction in the microvasculature of the skin. This property presumably relates to the amount of drug entering the skin[2] and thus becomes a possible basis for the comparison of drug delivery from two potentially equivalent topical corticosteroid formulations. Development of the methodology is attributed to Dr. R.B. Stoughton and Dr. A.W. McKenzie, who initially developed it as a means to assess potency of different topical corticosteroids.[3] Subsequently it was applied by pharmaceutical manufacturers and accepted by the Food and Drug Administration as a means of assessing bioavailability and bioequivalence. In these and other applications, it is referred to variously as the Stoughton-McKenzie test, the vasoconstrictor assay, or the skin blanching assay. Although there are many forms of the vasoconstrictor assay, the general method is

based on topical application of a corticosteroid-containing formulation for a period of 6 to 16 hours in healthy human subjects, followed by visual estimation by a trained, blinded observer of the degree of blanching on a multiple unit scale (0 - 3 or 0 - 4), at a single time point, usually two hours, after removal of the formulation. Most of the currently available generic topical corticosteroids have been approved on the basis of the vasoconstrictor assay as described in this paragraph, or a variant thereof, by OGD after consultation with the Division of Topical Drug Products. These studies were conducted prior to 1 July 1992.

The *Guidance* suggests conducting two *in vivo* studies - a pilot dose duration-response study and a pivotal *in vivo* bioequivalence study comparing test and reference products. The pilot study characterizes the dose duration-response relationship for the drug in terms of the E_{max} model (Section III) and is conducted solely with the reference listed drug (RLD). The dose duration method as recommended in this guidance for documentation of bioequivalence is based on three dose durations: ED_{50}, D_1 and D_2. The comparison of test and reference products in the pivotal study is conducted at a dose duration approximately equal to the population ED_{50} determined in the pilot study. Sensitivity in the pivotal study is established through dosing of the RLD calibrators at two dose durations, D_1 (the shorter dose duration calibrator) and D_2 (the longer dose duration calibrator). The guidance recommends that D_1 equal approximately 0.5 times ED_{50}, and D_2 equal approximately 2 times ED_{50} determined from the pilot study. Because each subject becomes a 'detector' in the study, only the data of those subjects whose D_2/D_1 ratio of pharmacodynamic responses meets a specified minimum value may be included in the data and statistical analyses supporting *in vivo* bioequivalence. The proposed methodology is more fully explained in subsequent sections of the guidance.

III. PHARMACODYNAMIC EFFECT STUDIES: THE VASOCONSTRICTOR ASSAY

Regulatory concerns regarding the vasoconstrictor assay, as it is currently performed, focus on two interrelated aspects of the methodology: 1) its validation and standardization as a bioassay; and 2) the use of a trained observer to measure vasoconstrictor response.

A. Validation and Standardization

Application of the vasoconstrictor assay to a determination of bioequivalence of a topical corticosteroid rests on the assumption that the vasoconstrictor properties of a topical corticosteroid can be utilized to establish a standard, validated bioassay. Development and validation of any assay, including a bioassay, involves certain documentation. Elements of this documentation that are of interest to scientists in the Center for Drug Evaluation and Research (CDER) were discussed at a December 1990 workshop cosponsored by the Food and Drug Administration, the American Association of Pharmaceutical Scientists, the Federation Internationale Pharmaceutique, the Canadian Health Protection Branch, and the Association of Official Analytical Chemists. A summary of the conclusions of this workshop has been published.[4]

In considering the following sections, the reader may find it useful to compare assay validation for a standard HPLC or GLC assay with validation for the vasoconstrictor bioassay. The latter method substitutes an observed pharmacodynamic response to an amount of drug, in this instance the vasoconstrictor response to a topical corticosteroid, for the detector response of an HPLC or GLC to a known amount of drug. Whereas only one instrument and detector are used in a standard blood or urine level assay, each subject in a pharmacodynamic bioassay study becomes the 'detector' responding to a known or unknown amount of drug. Despite many fundamental differences between a standard blood or urine level assay and a bioassay, many of the principles regarding standardization and validation are comparable. Several of these issues are discussed in the following sections.

1. Linearity

Understanding of basic pharmacodynamic relationships between either dose or concentration and a pharmacodynamic response of interest has expanded considerably over the last 15 years.[5] Application of this knowledge to the vasoconstrictor bioassay relates to an assessment of linearity. Although various models are available to express a relationship between drug dose and effect, one that may be especially useful to the vasoconstrictor bioassay is the E_{max} model, or the related sigmoid E_{max} model, which describes some measure of effect (E) in terms of a baseline effect (E_0), a maximal effect (E_{max}) and a dose (D) at which the effect is half-maximal (ED_{50}):

$$E = E_0 + \frac{E_{max} \times D}{ED_{50} + D}$$

The *in vivo* vasoconstrictor response generally approaches a maximum. Therefore, a primary issue requiring resolution in the application of the vasoconstrictor assay to assess bioequivalence is whether, at the strengths of the formulations to be tested in the assay, the capacity of the microvasculature of the skin to respond linearly has been exceeded. At relatively high strengths of a topical corticosteroid, minimal change in the vasoconstrictor response may occur, irrespective of increments in dose duration. At relatively low strengths of a topical corticosteroid, the question becomes one of determining the minimal dose that will produce a reliable and reproducible vasoconstrictor response. These questions are analogous to those confronted in the validation of an assay for drug levels in blood or urine, namely, to define the standard curve of an assay and the lower limit of sensitivity. Development and validation of a dose-response standard curve is essential to estimation of ED_{50}, D_1 and D_2.

In standard analytical methods validation, establishing linearity in detector response is necessary. Linearity in response is also desirable in the development of a vasoconstrictor assay. Because the intended generic and reference commercial formulations may be marketed at strengths that produce responses on the flat portion of the dose-response curve, the assay must be optimized to assure that the products are compared in the linear portion of the curve. Development of a dose-response relationship for a topical corticosteroid relies on some reliable way to administer a predetermined dose of the drug product to the skin. In the *Interim Guidance,*[5] three methods were postulated to be acceptable ways of reliably delivering a dose of topical corticosteroid: 1) the dose duration method; 2) the dilution method; and 3) the area method. Both the dose duration method and the dilution method showed promising results in agency sponsored studies.[6] From a formulation viewpoint, the dilution method is impractical, thus CDER scientists believe that the dose duration method is the most suitable for documentation of bioequivalence of topical corticosteroids. Development of a dose duration-response relationship for a topical corticosteroid will indicate points in the effect-time relationship at which the vasoconstrictor response becomes insensitive. In principle, the time course of response should be followed to return to baseline to insure that at each dose duration, the maximal pharmacodynamic response is observed.

2. Accuracy, Precision and Sensitivity

Development of methodology to establish the accuracy, precision, and sensitivity of a bioassay for a topical corticosteroid should be coincident with the development of an acceptable standard curve for the vasoconstrictor assay. This information, as well as the standard curve, should be developed for each study population. As with a standard blood or urine assay, this information will be developed through the use of untreated controls and calibrators containing the topical corticosteroid of interest. Replication of the untreated controls and calibrators will allow estimation of coefficients of variation. Just as a calibrator in a standard HPLC or GLC assay involves measurement of the detector response to a known concentration of drug substance, the calibrator for a pharmacodynamic topical corticosteroid bioassay, based on the dose duration method, involves application of a standard strength of a topical corticosteroid product for different periods of time.

B. Measurement of Vasoconstrictor Response

In an era with increasingly sophisticated methods to detect changes in light, temperature, pressure, and other physical and chemical changes, the use of a human observer to assess the magnitude of a pharmacodynamic effect becomes increasingly inadequate. Application of a commercially available chromameter (or colorimeter; e.g., Chroma Meter 200 or 300 model series,

Minolta) to detect erythema offers the possibility of replacing subjective visual scoring in the vasoconstrictor assay with objective, quantifiable measurements.[7,8] The Division of Bioequivalence currently considers the use of a chromameter to be applicable to bioequivalence studies based on the vasoconstrictor assay, and therefore recommends that pharmaceutical sponsors incorporate the use of a chromameter into their study designs. However, with acceptable validation, which includes establishing the correlation between chromameter measurements and visual estimation data, sponsors may rely on visual estimation of the degree of vasoconstriction.

C. Some Conclusions from Agency-Sponsored Studies

Results of vasoconstrictor assays conducted under agency contract have led OGD to conclude the following:

1. The chromameter possesses greater sensitivity to skin blanching than does visual estimation,

2. Skin blanching response measured over two consecutive 24 hour periods (48 hours) appears to follow a circadian pattern, possibly the result of a circadian pattern in plasma cortisol levels.[9,10] AUEC data through at least 24 hours from time of drug product removal or drug product application [Section IV(I)(9)], appear acceptable for bioequivalence comparisons, and

3. For baseline-adjusted, untreated control site-corrected AUEC data based on chromameter measurements, these studies suggest there is no strong indication of:

   a. a difference in response between left and right arms, or

   b. a location effect on the arm when skin sites are no closer than 3 - 4 cm to the antecubital fossa or to the wrist.

   Using the experimental design recommended in Section V(G)(2), in which the application pattern on each arm is complementary, e.g., T is complementary to R, the impact of such effects, should they occur, is minimized.

IV. PILOT DOSE DURATION-RESPONSE STUDY

The purpose of the pilot study is to determine the dose duration-response relationship of the topical corticosteroid to be studied in the pivotal *in vivo* bioequivalence study. The study is analogous to developing a standard curve in the assay of a drug in a biologic fluid matrix. The outcome of the pilot study provides the dose duration-response information necessary to determine the parameters ED_{50}, D_1, and D_2 to be used in the firm's pivotal *in vivo* bioequivalence study, and an estimation of the

proportion of subjects expected to meet the minimum D_2/D_1 ratio of AUEC values in the pivotal study. Because outcome of a pilot study may be a function of study conditions, including among other factors subject population characteristics, methodology used to assess skin blanching, and amount of drug product applied, this *Guidance* strongly encourages the performance of a pilot study by each study site for each reference listed drug (RLD) under investigation. Refer to Section IV(J)(3) regarding consultation with the Division of Bioequivalence concerning conduct and/or outcome of a pilot study.

A. Study Design and Analysis

1. Dose duration-response study based on RLD only, with randomization of dose duration skin sites.

2. Dose durations from 0.25 to 6.0 hours, plus untreated control sites on each arm to enable correction of active drug skin sites for color changes during the study unrelated to drug exposure. Because the vehicle corresponding to the RLD is not generally available, untreated control sites refer to untreated areas of skin, not to areas of skin to which vehicle has been applied.

3. Chromameter measurement of the pharmacodynamic response to the topical corticosteroid at various time periods, rather than a single time point measurement, following each dose duration application and removal.

4. Dose duration-response data should be modeled using either a nonlinear mixed effect modeling method or a naive pooled data method to determine the population ED_{50} value which will serve as the approximate dose duration for the bioequivalence comparison in the pivotal study.

5. Twelve subjects.

6. For products marketed in multiple strengths, the pilot and pivotal studies should be conducted on the high strength product.**

** Waiver of *in vivo* bioequivalence for lower strengths of a topical dermatologic corticosteroid product will be considered based on acceptable *in vivo* bioequivalence data for the high strength product and comparative formulation data which meet the qualitative sameness (Q_1) and quantitative sameness (Q_2) requirements of the Office of Generic Drugs' Inactive Ingredients Policy for the specific lower strength product relative to the comparable strength innovator product. If the inactive ingredients of the lower strength product do not meet the Q_1 and Q_2 requirements relative to the comparable strength innovator product, waiver will be considered with an explanation.

B. Subject Inclusion Criteria

1. Healthy subjects.

2. Subjects demonstrating adequate vasoconstriction to topical corticosteroids, i.e., 'responders' [Section IV(E)].

3. Written informed consent.

4. Willingness to follow study restrictions.

C. Subject Exclusion Criteria

1. Clinically significant hypertension or circulatory disease.

2. Individuals smoking within one week of study.

3. Caffeine intake greater than 500 mg per day prior to or during the study. (A cup of coffee contains about 85 mg of caffeine).

4. Clinically significant history of alcoholism or drug abuse.

5. Use of topical dermatologic drug therapy on ventral forearms, including prior dosing of a topical corticosteroid in a pharmacodynamic study to a particular skin site, within one month prior to the study.

6. Adverse reactions to topical or systemic corticosteroids.

7. Any current or past medical condition, including active dermatitis or any other dermatologic condition, which might significantly affect pharmacodynamic response to the administered drug.

8. Persons who would require shaving ventral forearms to insure consistent dose on skin surface.

9. Use of any vasoactive (constrictor or dilator) medication, prescription or OTC, that could modulate blood flow. Examples of such drugs include nitroglycerin, antihypertensives, antihistamines, NSAID's, aspirin, and OTC cough/cold products containing antihistamines and/or either phenypropanolamine or phentolamine.

10. Any obvious difference in skin color between arms.

D. Study Restrictions

1. No exercise with either arm, and no strenuous exercise overall, for study duration.

	VANOS Cream, *once daily* (n = 107)	Vehicle, *once daily* (n = 54)	VANOS Cream, *twice daily* (n = 107)	Vehicle, *twice daily* (n = 55)
Patients cleared	0 (0)	0 (0)	6 (6%)	0 (0)
Patients achieving treatment success*	19 (18%)	4 (7%)	33 (31%)	3 (6%)

*cleared or almost cleared

No efficacy studies have been conducted to compare VANOS (fluocinonide) Cream, 0.1% with any other topical corticosteroid product, including fluocinonide cream 0.05%.

INDICATIONS AND USAGE

VANOS (fluocinonide) Cream, 0.1%, is a corticosteroid indicated for treatment of plaque-type psoriasis affecting up to 10% body surface area (BSA). Use in patients under 18 years of age is not recommended because safety has not been established (see PRECAUTIONS: Pediatric Use section).

Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 60 g/week because the safety of VANOS Cream for longer than 2 weeks has not been established and because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Therapy should be discontinued when control of psoriasis has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

CONTRAINDICATIONS

VANOS Cream is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Use of more than one corticosteroid-containing product at the same time may increase total systemic glucocorticoid exposure.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA-axis suppression. This may be done by using cosyntropin ($ACTH_{1-24}$) stimulation testing. Patients should not be treated

2. No bathing or showering during the periods of drug application and assessment of skin blanching.

3. No use of creams, emollients, or similar products to forearms for 24 hours prior to and throughout the study.

E. Subject Screening for Response

1. Inclusion of 'nonresponders' reduces the ability of a study to detect true differences between test and reference products, should they exist. Therefore, for both the pilot dose duration-response study and the pivotal bioequivalence study, only 'responders,' i.e., subjects who have the capacity to vasoconstrict when dosed with the RLD used in the study, should be included.

2. In this *Guidance*, a 'responder' is defined as a subject who shows a response to a single dose duration of the RLD under the same occlusion or nonocclusion conditions used in the pilot and pivotal studies. Quantification of skin blanching in the pilot and pivotal studies by the chromameter is considered to be the most satisfactory. However, because of the discrete multiple unit scale (0 - 3 or 0 - 4) for visual readings, 'responder' status may be based on visual readings. A dose duration of 4 hours (based on a potency group III product,[3] with the results shown in Figure AIII.1), or 6 hours[11] is suggested, with skin blanching assessment 2 hours following drug product removal. A 'responder' shows a visual reading of at least one unit.

3. To conserve skin sites on the forearm for use in the dose duration-response study or bioequivalence study, 'responder' status may be based on studies conducted at sites other than the forearm.

4. Criteria for identification of responders, including dose duration, magnitude of response, and skin site tested, should be included in the study report. Responder status may also be documented from participation in a previous vasoconstrictor assay study.

F. Validation of Assay Precision

Validation of intraspot and interspot precision of the assay methodology should be documented in four to six subjects who meet the criteria and restrictions of Sections IV(B - D). Four untreated control sites on each ventral forearm should be selected. Four chromameter readings of each site should be made within a one hour period.

The validation study documents acceptable precision by the bioequivalence testing firm in utilizing the chromameter for the measurement of skin blanching. The study should be conducted prior to administration of the drug product.

Results should be provided in the pilot study report, if submitted [Section IV)(J)(3)], and in the pivotal *in vivo* bioequivalence study report.

G. Occlusion versus Nonocclusion

Class labeling for topical corticosteroids states that occlusive film may be used for the management of psoriasis or recalcitrant conditions. This statement may be found in labeling of certain products representing all potency groups, although labeling for certain high potency products specifically states that occlusive films are not to be used. Provided occlusion is allowed in the labeling of the specific reference listed drug, the pilot dose duration-response study and pivotal *in vivo* bioequivalence study may be conducted using occlusive film. However, caution must be used, as analyses of pilot studies conducted under agency contract suggest that the ED_{50} (the dose duration to be used in the pivotal study) decreases with increasing topical corticosteroid product potency.[12] Evaluation of dose duration-response requires dose duration data at times less than the ED_{50}. Very short dose durations are difficult to conduct experimentally and tend to produce high variability in response. Thus occlusion may be appropriate only for the lower potency products, e.g., potency groups VI and VII. If occlusion is used for the pilot study, it should also be used for the pivotal study.

H. Methods of Application and Removal

Either of two methods of application and removal may be utilized in the pilot and pivotal studies [Section V(G)(3)]:

1. Staggered application with synchronized removal, in which drug is applied to skin sites at different times and removed at the same time (Appendix I), and;

2. Synchronized application with staggered removal, in which drug is applied to skin sites at the same time and removed at different times (Appendix II).

I. Study Day Activities

1. Subjects should begin the study sessions at approximately the same time each study day (within one hour).

2. Verification by history of adequate washout of excluded drugs.

3. The forearm should be free of any dirt or particulate matter that would interfere with proper drug application or assessment of pharmacodynamic response. Cleansing of the skin is not encouraged because of the possible effects on drug uptake and pharmacodynamic response to the drug product. If necessary, cleansing should be

performed not less than two hours prior to drug product application. If cleansing is performed, this should noted in the study report.

4. Whether the study is conducted under occlusion or nonocclusion conditions, use of a protective, nonocclusive guard to prevent smearing or removal of topical drug product from the skin site. Care should be taken to avoid contact between the guard and any drug product to prevent inadvertent contamination of untreated control sites or other test sites.

5. Skin sites should be no closer than 3 - 4 cm to the antecubital fossa or to the wrist.

6. Application of the RLD to skin sites of identical surface area on the ventral forearms. Suggested dose durations for the pilot study are 0.25, 0.5, 0.75, 1, 1.5, 2, 4 and 6 hours, but may vary depending on the corticosteroid under investigation.

   a. Eight dose durations, i.e., active drug sites, should be equally divided between the two arms.

   b. Amount of drug product, skin site size, and spacing between sites should be determined by the testing laboratory. For reference, some investigators have used doses of 2 - 10 mg of formulation per cm^2 of skin surface area, and 1 cm diameter sites. Sites may be spaced as close as 2.5 cm center-to-center, and may be in a straight line or staggered pattern, depending on skin surface suitability (e.g., vascularity, nevi, etc.) and arm length. If vasoconstrictor effects of two adjacent test sites overlap and the investigator cannot discern between the vasoconstrictor effect at each test site, the subject should be excluded from the data analysis.

7. Use of two untreated control skin sites per arm for studies based on chromameter measurements.

   a. Application to each subject of eight dose durations [Section IV(I)(6)] and four untreated control sites should be randomly assigned among the 12 sites, maintaining two untreated control sites and four dosed sites on each arm (six sites per arm).

   b. Studies based on visual scoring do not require untreated control sites because the reading involves a visual comparison of the treated site to the surrounding skin. Application to each subject of eight dose durations should be randomly assigned between the two arms, maintaining four dosed sites on each arm.

8. Prior to measurement of the pharmacodynamic response at the end of the application period, remaining topical corticosteroid should be gently removed from the skin. This may be accomplished by either of the methods below.

   a. Three consecutive swabbings with dry cotton swabs.

      Suitable for either the staggered application with synchronized removal method, or the synchronized application with staggered removal method.

   b. Washing all skin sites with mild skin cleanser and water, blotting the sites dry with a nonabrasive towel, and allowing to air-dry for at least five minutes prior to evaluation. If after five minutes the subject has any visible cutaneous effects related to washing, a longer waiting period may be necessary.

      i. Suitable for the staggered application with synchronized removal method.

      ii. Cleanse arm surfaces with a minimum amount of skin cleanser, for example one drop of a liquid cleanser worked to a lather in wetted hands, followed by rinsing.

      iii. Examples of mild liquid skin cleansers are Purpose® Gentle Cleansing Wash (Johnson & Johnson), and Cleansing Wash (Neutrogena).

9. Assessment of baseline skin color and skin blanching at each site. Examples of assessment time periods are:

   a. For staggered application with synchronized removal:

      For all dose durations and untreated control sites, baseline readings within one hour prior to drug application of the longest dose duration, and at 0, 2, 4, 6, 19, and 24 hours after drug product removal (Appendix I).

      Time zero equals time of drug product removal.

   b. For synchronized application with staggered removal:

      For all dose durations and untreated control sites, baseline readings within one hour prior to the time of drug application to active drug sites, and 6, 8, 11, 24, and 28 hours after drug product application (Appendix II).

      Time zero equals time of drug product application.

Note: Optimal assessment times for either method of application and removal may require adjustment of these schedules for the particular drug product and study site. For either method, at least one reading should be scheduled between 5 PM and midnight.

J. Data Analyses and Pharmacodynamic Modeling

1. Chromameter Data

a. Adjust the chromameter raw data of each skin blanching response versus time profile (both active drug sites and untreated control sites) for the baseline value at that site. Correct each baseline-adjusted active drug site for the mean of the two baseline-adjusted untreated control sites on the same arm (Tables AIII.1 - AIII.3).

b. Using the trapezoidal rule, compute the area under the effect curve (AUEC) for each baseline-adjusted, untreated control site-corrected dose duration (Tables AIII.3, AIII.4):

i. $AUEC_{(0\text{-}24)}$ for the staggered application with synchronized removal method, or

ii. $AUEC_{(5\text{-}28)}$ for the synchronized application with staggered removal method (based on the dose duration schedule of Section IV(I)(6)]. In the general case, AUEC from the longest dose duration to 28 hours after drug product application is computed.

c. Fitting dose duration-response data by averaging across subjects at each dose duration is not acceptable. Rather, the data should be fit by using all observations of all individual subjects simultaneously. The modeling software should provide ED_{50} and E_{max} values for the data pooled from 12 subjects. The following methods are acceptable:

i. Fitting based on the assumption of a nonlinear mixed effect model (population model) using suitable software (Figure AIII.1). The mixed effect modeling technique accounts for within- and among-subject variability, or

ii. Fitting based on nonlinear least squares regression, pooling individual observations from all subjects (naive pooled data method).

d. Determine the ED_{50} (the dose duration corresponding to half-maximal response).

e. Determine D_1 and D_2 corresponding to approximately one-half ED_{50} and two times ED_{50}, respectively, for use in the pivotal study.*** These values bracket ED_{50}, correspond to approximately 33% and 67% respectively of the maximal response, and represent the sensitive portion of the dose duration-response curve.[5]

2. Visual Data (refer to Section III(8))

a. Compute the area under the effect curve (AUEC) for each vasoconstriction time profile.

b. Fit the dose duration-response data as described in Section IV(J)(1)(c).

c. Determine the ED_{50}, D_1, and D_2.

3. Consultation with the Division of Bioequivalence

If a sponsor wishes to discuss issues related to assay validation, dose duration-response, or other aspects of its pilot dose duration-response study prior to the conduct of the pivotal *in vivo* bioequivalence study, the sponsor has the option to submit the study data and summary results of the pilot study to the Division of Bioequivalence for review of ED_{50}, D_1, and D_2 values, and the proposed pivotal study protocol. If the pilot study results are submitted, the firm may wish to include all study data, with an explanation accompanying any data not included in the pharmacodynamic analysis.

Sponsors may consider that they have sufficient information about the dose duration-response relationship of the topical corticosteroid under investigation to proceed directly to the pivotal study without conduct of the pilot study. This course of action assumes knowledge of ED_{50}, D_1, and D_2 appropriate to the RLD under study site conditions, which is essential to an acceptable pivotal study. Staff in the Division of Bioequivalence are available to review this information at the request of a sponsor.

*** The observed ED_{50} value may be rounded by up to 15 minutes to obtain the ED_{50} value used in the pivotal study. In practice, a demonstration of dose duration-response based on D_1 within 0.25 - 0.5 times the observed ED_{50} and D_2 within 2 - 4 times the observed ED_{50} is acceptable. For potent corticosteroids with short ED_{50} values, these recommendations may require adjustment. If so, the Division of Bioequivalence may be consulted.

4. Computer Formatted Data Submission

If the study data and summary results are submitted, a diskette in the ASCII format containing the study data should be submitted with the pilot study. Chromameter raw data; baseline-adjusted data; baseline-adjusted, untreated control site-corrected data; and AUEC data should be arranged in separate files in the format given in Tables AIII.1 - AIII.4.

V. PIVOTAL *IN VIVO* BIOEQUIVALENCE STUDY

The purpose of the pivotal study is to document *in vivo* bioequivalence of the test product to the reference listed drug (RLD). The guidance specifies the minimum dose duration-response ratio which must be met by individual subjects for inclusion in the data analysis. Therefore, a pivotal study may generally be initiated without consultation with the Division of Bioequivalence [Section IV(J)(3)].

A. Study Design

1. Pharmacodynamic bioequivalence study using within-study day replicate single dose durations of test and reference products, and based on the population ED_{50} identified in the pilot study.

2. Individual subject dose duration-response, based upon an acceptable D_2/D_1 ratio of AUEC values of the RLD. The minimum value of the ratio should be 1.25. Success in meeting this dose duration-response criterion will be determined through duplicate dosing of the RLD at D_1, the dose duration equal to approximately 0.5 times the population ED_{50}, and at D_2, the dose duration equal to approximately 2 times the population ED_{50}.

3. Forty to sixty evaluable subjects, i.e., subjects who meet the 'responder' and 'detector' criteria of Sections IV(E) and V(H)(1)(c).

B. Subject Inclusion Criteria

Consult Section IV(B).

C. Subject Exclusion Criteria

Consult Section IV(C).

D. Study Restrictions

Consult Section IV(D).

E. Subject Screening for Response

Consult Section IV(E).

F. Assay Precision

Consult Section IV(F).

G. Study Day Activities

1. Consult Section IV(I), where applicable.

2. Application of dose durations to skin sites on the ventral forearms of each subject should be randomly assigned, maintaining the recommendations described below. Sites may be occluded or nonoccluded, based on the considerations of Section IV(G) and the pilot study results. Untreated control skin sites should also be included for studies based on chromameter measurements. Dose durations and control sites on each arm should include:

   T: the test product at the dose duration corresponding approximately to ED_{50}, as determined with the reference listed drug (RLD) in the pilot study (two sites per arm);

   R: the reference listed drug (RLD) at the same dose duration corresponding approximately to ED_{50} as for the test product T (two sites per arm);

   D_1: the shorter dose duration RLD calibrator (one site per arm);

   D_2: the longer dose duration RLD calibrator (one site per arm); and

   UNT: the untreated control (two sites per arm).

   The total number of testing sites is 16 (eight sites per arm). The eight treatments should be randomized, as noted above. Application patterns on each arm should be complementary, i.e., D_2 is complementary to D_1, R is complementary to T, and UNT is complementary to UNT. As examples, where T is assigned a specific skin site location on one arm, R should be assigned to the corresponding skin site on the other arm. Where UNT is assigned a specific skin site location on one arm, UNT should be assigned to the corresponding skin site on the other arm.

A representative application sequence for a particular subject might be:

ANTECUBITAL FOSSA

Left Arm	Right Arm
D_1	D_2
T	R
UNT	UNT
R	T
UNT	UNT
T	R
D_2	D_1
R	T

WRIST

The specific pattern of skin sites, i.e., medial (ulnar) to lateral (radial), and superior to inferior, should be described by the firm.

3. Either the staggered application with synchronized removal or the synchronized application with staggered removal method, consistent with the methodology used in the pilot study, should be used for D_1, D_2, and ED_{50} dose durations.

4. Examples of time periods for assessment of baseline skin color and skin blanching at each site are:

   a. For staggered application with synchronized removal:

      For all dose durations and untreated control sites, baseline readings within one hour prior to drug application of the longest dose duration; skin blanching readings at 0, 2, 4, 6, 19, and 24 hours after drug product removal. Actual times will depend upon the time of dosing and the topical corticosteroid being studied.

      Time zero equals time of drug product removal.

   b. For synchronized application with staggered removal:

      For all dose durations and untreated control sites, baseline readings within one hour prior to the time of drug application to active drug sites; skin blanching readings at the following times

after drug product application: D_2 (see Note below), 6, 8, 11, 24, and 28 hours. Actual times will depend upon the time of dosing, the topical corticosteroid being studied, and D_2.

Time zero equals time of drug product application.

Note: For example, if D_2 for a specific drug product equals 4 hours, the first post-baseline reading of all skin sites, both active drug sites and untreated control sites, would be at 4 hours. For either method, at least one reading should be scheduled between 5 PM and midnight.

H. Data and Statistical Analyses

1. Data Analysis

a. For the chromameter raw data, adjust each skin blanching response versus time profile (both active drug sites and untreated control sites) for the baseline value at that site. Correct the data of each baseline-adjusted active drug site for the mean of the two baseline-adjusted untreated control sites from the same arm (Tables AIV.1 - AIV.4).

b. Compute AUEC for each baseline-adjusted, untreated control site-corrected dose duration (Tables AIV.3, AIV.5, AIV.6).

i. $AUEC_{(0\text{-}24)}$ for the staggered application with synchronized removal method, or

ii. AUEC from time D_2 to 28 hours, $AUEC_{(D2\text{-}28)}$, for the synchronized application with staggered removal method.

c. Only the data of 'detectors,' i.e., individual subjects whose AUEC values (Table AIV.5) at D_1 and D_2 are both negative and that meet the dose duration-response criterion below, should be included in the data analysis (Tables AIV.6, AV.1). The dose duration-response criterion is:

$$\frac{AUEC \ \ at \ \ D_2}{AUEC \ \ at \ \ D_1} \geq 1.25$$

where:

AUEC at D_2 = 0.5 [AUEC at D_2 (left arm) + AUEC at D_2 (right arm)];

AUEC at D_1 = 0.5 [AUEC at D_1 (left arm) + AUEC at D_1 (right arm)].

d. Only those subjects with a complete data set, i.e., duplicate values of D_1 and D_2, and quadruplicate values of T, R, and UNT, should be included in the data analysis.

e. The bioequivalence comparison should be based on AUEC values computed according to Section V(H)(1)(b) at the dose duration corresponding approximately to ED_{50} [treatments T and R, Section V(G)(2)].

f. All study data, including the data of 'nondetectors,' should be submitted. An explanation (e.g., 'nondetector,' overlap of vasoconstrictor effect due to an adjacent site, etc.) should accompany any data not used in the bioequivalence evaluation.

2. Statistical Analysis

a. The statistical analysis requires the use of untransformed data because AUEC values of treatments T and R, calculated from baseline-adjusted, untreated control site-corrected data, although generally negative, are sometimes positive. The presence of both positive and negative data eliminates the use of conventional statistical transformations. Previously used approximate methods,[13] for example calculating a confidence interval for the difference between test and reference product averages, and dividing these limits by an estimate of the reference product average, are not applicable. Locke's method[14] provides an exact confidence interval from untransformed data.

b. The 90% confidence interval should be calculated for the ratio of the average AUEC response due to the test product (average of four replicates) to the average AUEC response due to the reference product (average of four replicates) using Locke's method. The formulae and a worked example, based on the data of Table AIV.6, are given in Appendix V.

c. The Office of Generic Drugs has not determined at this time the equivalence interval for bioequivalence. The Office recognizes that an equivalence interval wider than 80-125%, as a public standard, may be necessary pending evaluation of data submitted to the agency.

d. The randomization code, indicating the specific skin sites to which each dose duration and control site was assigned, should be submitted with the study report.

3. Computer Formatted Data Submission

A diskette in the ASCII format containing the study data should be submitted with the application. Chromameter raw data; baseline-adjusted data; baseline-adjusted, untreated control site-corrected data; and AUEC data should be arranged in separate files in the format given in Tables AIV.1 - AIV.6.

Prepared by: Wallace P. Adams Date: 2 June 1995

Wallace P. Adams, Ph.D.
Reviewer
Division of Bioequivalence

Date: June 2, 1995

Gur Jai Pal Singh, Ph.D.
Reviewer
Division of Bioequivalence

Concur: Date: 6/2/95

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

Concur: Date: 6/2/95

Lawrence J. Lesko, Ph.D.
Associate Director for Research
Office of Generic Drugs

Concur: Date: June 2 1995

Roger L. Williams, M.D.
Associate Director for Science and
Medical Affairs
Center for Drug Evaluation and Research

REFERENCES

1. Shah VP. Interim guidance, topical corticosteroids: *in vivo* bioequivalence and *in vitro* release methods. Division of Bioequivalence and Division of Anti-Infective Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD: 1 July 1992.

2. Pershing LK, Silver BS, Krueger GG, Shah VP, Skelley [sic] JP. Feasibility of measuring the bioavailability of topical betamethasone dipropionate in commercial formulations using drug content in skin and a skin blanching bioassay. Pharm Res 1992;9:46-51.

3. Stoughton RB. Vasoconstrictor assay - specific applications. In: Maibach HI, Surber C, eds. Topical corticosteroids. Basel: Karger, 1992:42-53.

4. Shah VP, Midha KK, Dighe S, et al. Conference report. Analytical methods validation: bioavailability, bioequivalence and pharmacokinetic studies. Pharm Res 1992;9:588-92.

5. Holford NHG, Sheiner LB. Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokin 1981; 6:429-53.

6. Pershing LK, Lambert L, Wright ED, Shah VP, Williams RL. Topical 0.050% betamethasone dipropionate: pharmacokinetic and pharmacodynamic dose-response studies in humans. Arch Dermatol 1994;130:740-7.

7. Queille-Roussel C, Poncet M, Schaefer H. Quantification of skin-colour changes induced by topical corticosteroid preparations using the Minolta Chroma Meter. Br J Dermatol 1991;124:264-70.

8. Elsner P. Chromametry: hardware, measuring principles, and standardization of measurements. In: Berardesca E, Elsner P, Maibach HI, eds. Bioengineering of the skin: cutaneous blood flow and erythema. Boca Raton: CRC Press, 1995:247-52.

9. Krieger DT, Allen W, Rizzo F, Krieger HP. Characterization of the normal temporal pattern of plasma corticosteroid levels. J Clin Endocrinol Metab 1971;32:266-84.

10. Pershing LK, Corlett JL, Lambert LD, Poncelet. Circadian activity of topical 0.05% betamethasone dipropionate in human skin *in vivo*. J Invest Dermatol 1994;102:734-9.

11. Smith EW, Meyer E, Haigh JM, Maibach HI. The human skin blanching assay as an indicator of topical corticosteroid bioavailability and potency: an update. In Bronaugh RL, Maibach HI, eds. Percutaneous absorption: mechanisms-methodology-drug delivery. 2nd ed. New York: Marcel Dekker, 1989:443-60.

12. Singh GJP, Lesko LJ, Shah VP, et al. Bioequivalence methodology for dermatologic corticosteroids based on pharmacodynamic modeling [Abstract]. Clin Pharmacol Ther 1995;57:181.

13. Schuirmann DJ. Confidence intervals for the ratio of two means from a crossover study. In: Proceedings of the biopharmaceutical section, American Statistical Association, Washington, DC 1989; 121-6.

14. Locke CS. An exact confidence interval from untransformed data for the ratio of two formulation means. J Pharmacokinet Biopharm 1984;12:649-55.

APPENDIX I

STAGGERED APPLICATION WITH SYNCHRONIZED REMOVAL: SCHEMATIC FOR A SUGGESTED PILOT STUDY PROTOCOL

Figure AI.1

Baseline (BL) Measurement, Drug Application and Drug Removal

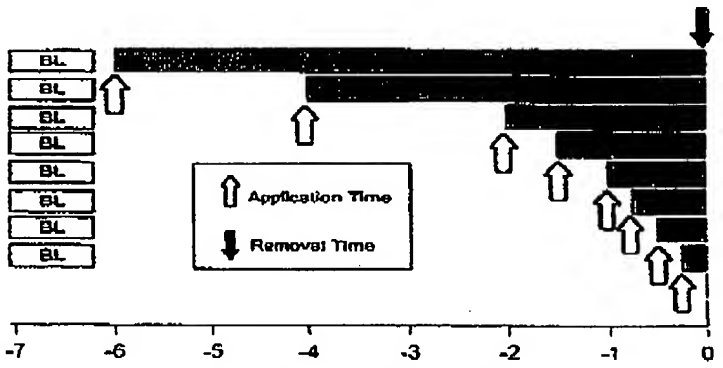
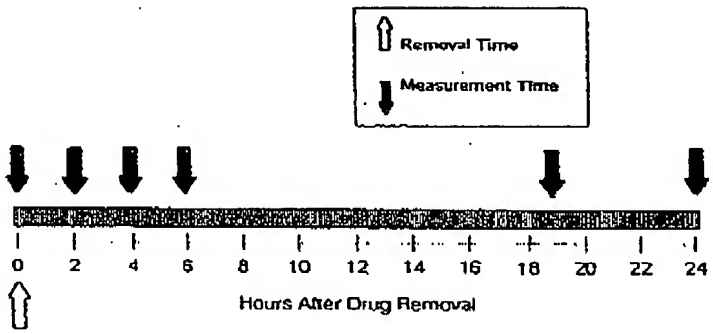


Figure AI.2

Skin Blanching Measurements



APPENDIX II

SYNCHRONIZED APPLICATION WITH STAGGERED REMOVAL: SCHEMATIC FOR A SUGGESTED PILOT STUDY PROTOCOL

Figure AII.1

Baseline (BL) Measurement, Drug Application and Drug Removal

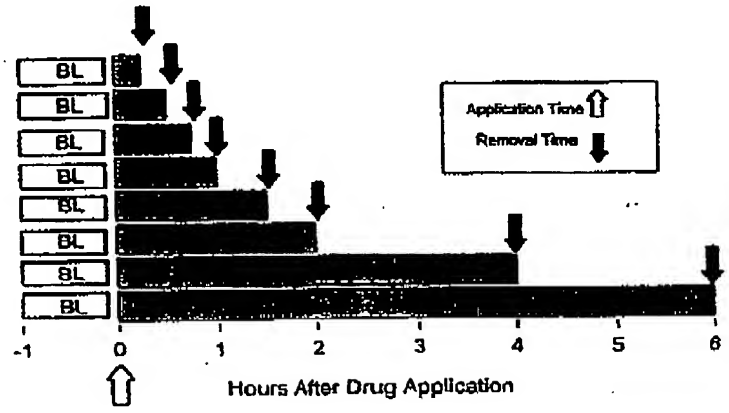
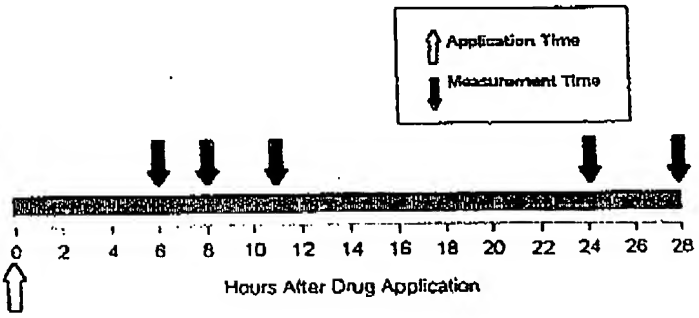


Figure AII.2

Skin Blanching Measurements



APPENDIX III

ANALYSIS OF DATA FROM AN AGENCY-SPONSORED PILOT STUDY: AN EXAMPLE

Development of the recommended study designs in this guidance included the conduct in late 1994 and early 1995 under agency contract [Section III(C)] of small-scale vasoconstrictor assays at two research sites: the University of Utah Health Sciences Center and the University of California, San Diego, School of Medicine. The University of Utah study used the synchronized application with staggered removal method, while the University of California study used the staggered application with synchronized removal method. Each research site conducted a pilot dose duration-response study and a 'pivotal' *in vivo* bioequivalence study, with 12 subjects in each of the four studies. The contract studies differed in several ways from those recommended in this guidance. The contract studies (1) used untreated control sites corresponding to each active drug site, (2) measured skin blanching through 48 hours, and (3) did not replicate the test and reference products on each arm ('pivotal' study).

No preference in methodology is intended by use of data based on the staggered application with synchronized removal method in Appendices III - V to illustrate data analysis. Either method of application and removal is acceptable. Table AIII.1 presents chromameter a-scale raw data of the University of California pilot study for subject 1 through 24 hours. Baseline-adjusted data are presented in Table AIII.2, and baseline-adjusted, untreated control site-corrected data are presented in Table AIII.3. In this example data set, each active drug site was corrected for its corresponding untreated control site. However, the guidance recommends use of only two untreated control sites per arm, and subtracting their average from all active drug sites on that arm. Table AIII.4 presents $AUEC_{(0-24)}$ data for all subjects and dose durations. The E_{max} model fit to the pooled data is shown in Figure AIII.1.

Table AIII.1 Chroma Meter (Minolta) a-scale readings for a subject

SUB	DD	SITE	BL	Hours after drug removal					
				0	2	4	6	19	24
1	0.25	UNT	9.86	9.99	10.10	9.52	10.03	10.40	9.65
1	0.25	TRT	10.36	9.89	10.38	10.32	10.51	10.86	10.04
1	0.5	UNT	9.27	8.20	9.78	8.54	9.61	9.87	9.59
1	0.5	TRT	9.59	8.77	9.35	9.27	8.78	10.40	9.82
1	0.75	UNT	8.45	8.75	8.24	8.16	8.92	8.43	8.22
1	0.75	TRT	8.46	8.66	8.53	8.04	8.26	8.72	8.56
1	1	UNT	9.00	9.63	8.45	8.03	8.94	9.33	9.66
1	1	TRT	8.52	8.80	8.87	8.53	8.05	8.66	8.21
1	1.5	UNT	9.44	9.39	9.46	9.27	9.92	9.59	9.01
1	1.5	TRT	9.59	9.60	9.99	9.93	9.18	10.23	9.24
1	2	UNT	10.12	10.13	9.50	9.93	9.39	10.95	10.84
1	2	TRT	10.28	10.25	10.68	10.15	10.31	11.46	8.92
1	4	UNT	8.89	8.01	8.78	8.89	9.76	8.48	9.18
1	4	TRT	8.21	8.28	8.36	7.98	7.96	8.15	8.30
1	6	UNT	9.18	9.46	8.79	8.03	9.29	10.11	9.51
1	6	TRT	9.37	9.61	9.30	8.92	9.20	10.16	9.63

Appendix III abbreviations appear on page 28.

Table AIII.2 Baseline-adjusted a-scale data for a subject

SUB	DD	SITE	BL	Hours after drug removal					
				0	2	4	6	19	24
1	0.25	UNT	-	0.13	0.24	-0.34	0.17	0.54	-0.21
1	0.25	TRT	-	-0.47	0.02	-0.04	0.15	0.50	-0.32
1	0.5	UNT	-	-1.07	0.51	-0.73	0.34	0.60	0.32
1	0.5	TRT	-	-0.82	-0.24	-0.32	-0.81	0.81	0.23
1	0.75	UNT	-	0.30	-0.21	-0.29	0.47	-0.02	-0.23
1	0.75	TRT	-	0.20	0.07	-0.42	-0.20	0.26	0.10
1	1	UNT	-	0.63	-0.55	-0.97	-0.06	0.33	0.66
1	1	TRT	-	0.28	0.35	0.01	-0.47	0.14	-0.31
1	1.5	UNT	-	-0.05	0.02	-0.17	0.48	0.15	-0.43
1	1.5	TRT	-	0.01	0.40	0.34	-0.41	0.64	-0.35
1	2	UNT	-	0.01	-0.62	-0.19	-0.73	0.83	0.72
1	2	TRT	-	-0.03	0.40	-0.13	0.03	1.18	-1.36
1	4	UNT	-	-0.88	-0.11	0.00	0.87	-0.41	0.29
1	4	TRT	-	0.07	0.15	-0.23	-0.25	-0.06	0.09
1	6	UNT	-	0.28	-0.39	-1.15	0.11	0.93	0.33
1	6	TRT	-	0.24	-0.07	-0.45	-0.17	0.79	0.26

Table AIII.3 Baseline-adjusted, untreated control site-corrected a-scale data and $AUEC_{(0\text{-}24)}$ data for a subject

SUB	DD	SITE	BL	Hours after drug removal						$AUEC_{(0\text{-}24)}$*
				0	2	4	6	19	24	
1	0.25	TRT	-	-0.60	-0.22	0.30	-0.02	-0.04	-0.11	-1.23
1	0.5	TRT	-	0.25	-0.75	0.41	-1.15	0.21	-0.09	-7.39
1	0.75	TRT	-	-0.10	0.28	-0.13	-0.67	0.28	0.33	-1.48
1	1	TRT	-	-0.35	0.90	0.98	-0.41	-0.19	-0.97	-3.80
1	1.5	TRT	-	0.06	0.38	0.51	-0.89	0.49	0.08	-0.23
1	2	TRT	-	-0.04	1.02	0.06	0.76	0.35	-2.08	5.77
1	4	TRT	-	0.95	0.26	-0.23	-1.12	0.35	-0.20	-4.74
1	6	TRT	-	-0.04	0.32	0.70	-0.28	-0.14	-0.07	-1.53

* $AUEC_{(0\text{-}24)}$ units are baseline-adjusted, untreated control site-corrected a-scale units times hours

Table AIII.4 $AUEC_{(0-24)}$ data of all 12 subjects at each dose duration

DD	Subject Number					
	1	2	3	4	5	6
0.25	-1.23	-0.02	-13.87	-27.27	-10.65	-10.41
0.5	-7.39	-5.13	-15.03	-3.71	7.72	-5.94
0.75	-1.48	-8.92	-18.39	-43.82	-23.42	-2.29
1	-3.80	-24.56	-16.25	-44.39	-20.37	-8.92
1.5	-0.23	-19.21	-15.44	-77.04	-19.95	-20.64
2	5.77	-1.80	-23.74	-66.80	-32.00	-19.52
4	-4.74	-43.07	-24.80	-62.96	-32.81	-8.52
6	-1.53	-41.56	-21.79	-71.60	-61.51	-19.01

DD	Subject Number					
	7	8	9	10	11	12
0.25	4.20	-11.95	-12.36	1.15	-30.03	-7.25
0.5	-12.31	7.45	12.95	-39.45	-39.56	14.73
0.75	1.34	6.95	1.88	-40.68	-61.06	-21.09
1	-18.84	8.78	-43.35	-16.19	-43.58	10.81
1.5	-42.70	1.26	-20.97	6.87	-40.73	0.51
2	-37.29	-48.83	-39.79	10.75	-82.01	-10.51
4	-45.46	-71.77	-57.55	-37.64	-27.82	-14.89
6	-37.24	-8.14	-34.18	-35.01	-33.60	16.14

Abbreviations in Tables AIII.1 - AIII.4

DD: Dose duration in hours
UNT: Untreated control site (no product applied)
TRT: Treated site (topical corticosteroid product applied)
BL: Baseline measurement of skin color, as described in Section IV(I)(9)

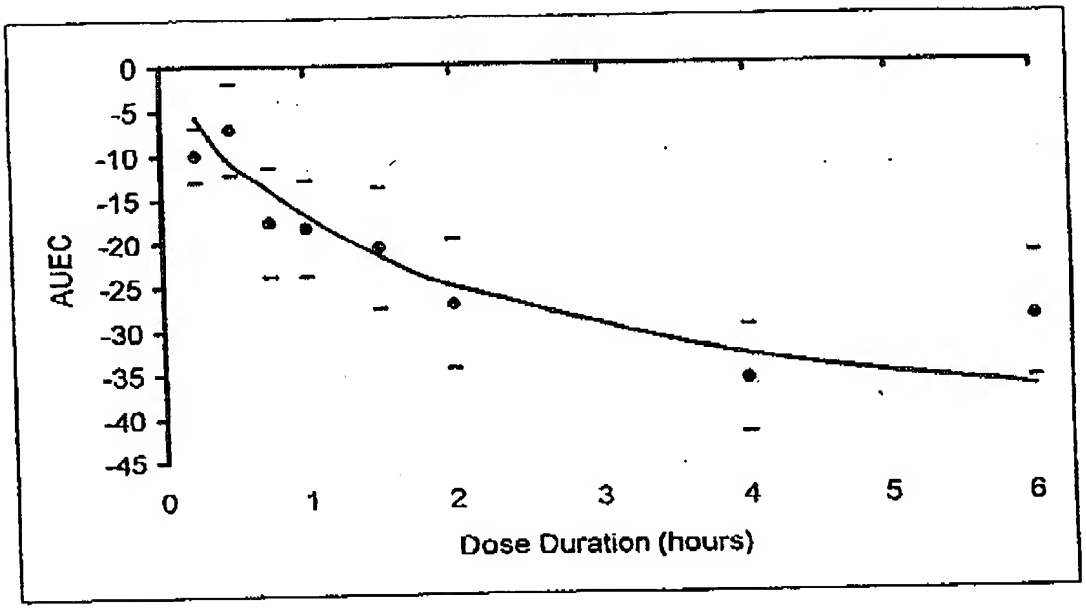


Figure AIII.1 Observed $AUEC_{(0\text{-}24)}$ mean (filled circles) and SEM (upper and lower limits), and E_{max} model fitted (solid line) to the pooled dose duration-response data of all 12 subjects in the pilot study.

Note 1: Data are baseline-adjusted and untreated control-site corrected, thus AUEC was set to zero at dose duration equal to zero.

Note 2: The E_{max} model fit (solid line) was determined using a population pharmacokinetic-dynamic data modeling program (P-Pharm, Simed). The fitted population values were:

ED_{50}:	1.89 hours
E_{max}:	-48.80 a-scale units times hours

Note 3: Based on these data, the dose durations selected as the approximate ED_{50} for the comparison of test and reference products, and as D_1 and D_2 in the 'pivotal' *in vivo* bioequivalence study were:

Approximate ED_{50}:	2.0 hours
D_1:	1.0 hour
D_2:	4.0 hours

APPENDIX IV

ANALYSIS OF DATA FROM AN AGENCY-SPONSORED 'PIVOTAL' STUDY: AN EXAMPLE

Appendix IV presents chromameter a-scale data and $AUEC_{(0-24)}$ data of the University of California 'pivotal' *in vivo* bioequivalence study referred to in Appendix III. In the 'pivotal' study, the bioequivalence comparison is based on the dose duration-response analysis summarized in Figure AIII.1, Note 3. Table AIV.1 presents the a-scale raw data through 24 hours for subject 1. Baseline-adjusted data are presented in Table AIV.2, and baseline-adjusted, untreated control site-corrected data are presented in Table AIV.3. In this example data set, each active drug site was corrected for its corresponding untreated control site. However, the guidance recommends use of only two untreated control sites per arm, and subtracting their average from all active drug sites on that arm. Table AIV.4 presents the baseline-adjusted and untreated control site-corrected a-scale data for test and reference products for all subjects. Table AIV.5 presents right and left arm $AUEC_{(0-24)}$ data, and the two arm average data, for D_1 and D_2 for all subjects. Table AIV.5 also identifies 'detectors,' i.e., evaluable subjects, defined as those subjects who met the dose duration-response criterion [Section V(H)(1)(c)]. Table AIV.6 presents right and left arm $AUEC_{(0-24)}$ data, and the two arm average data, for test and reference products for all subjects at a dose duration of 2.0 hours, and highlights the two arm average $AUEC_{(0-24)}$ data of the 'detectors.' Only the data of 'detectors' are included in the analysis for bioequivalence, as described in Appendix V.

Table AIV.1 Chroma Meter (Minolta) a-scale raw data for a subject

SUB	TRT	ARM	LOC	SITE	BL	Hours after drug removal					
						0	2	4	6	19	24
1	A	R	1	UNT	7.34	7.23	8.09	7.64	7.82	7.68	8.71
1	A	R	1	TRT	7.11	7.86	7.59	5.92	6.23	6.32	7.30
1	B	R	2	UNT	6.18	7.38	7.26	6.85	7.35	7.14	7.87
1	B	R	2	TRT	6.79	6.29	6.12	4.45	5.88	6.01	7.26
1	C	R	3	UNT	6.28	7.32	7.80	6.77	7.75	6.59	7.55
1	C	R	3	TRT	7.78	9.26	9.30	7.42	8.24	7.40	8.59
1	D	R	4	UNT	9.31	10.19	10.61	9.56	10.88	9.52	10.13
1	D	R	4	TRT	7.38	8.22	6.94	5.07	6.98	7.24	7.91
1	C	L	1	UNT	7.62	7.98	7.56	7.48	7.24	6.73	7.49
1	C	L	1	TRT	6.97	5.42	5.39	4.39	4.79	5.76	6.45
1	B	L	2	UNT	7.12	6.32	6.76	6.25	6.74	6.80	7.58
1	B	L	2	TRT	7.46	4.48	4.38	4.11	4.39	6.27	7.25
1	A	L	3	UNT	7.69	7.03	7.73	7.21	7.87	7.89	8.38
1	A	L	3	TRT	8.99	8.75	8.07	6.74	6.53	7.14	8.25
1	D	L	4	UNT	8.99	8.28	8.95	8.50	9.10	9.05	9.93
1	D	L	4	TRT	8.80	8.04	6.71	5.51	5.14	7.05	7.96

TRT A: RLD at dose duration D_1 (1.0 hour)
TRT B: RLD at dose duration D_2 (4.0 hours)
TRT C: Test drug product at dose duration of 2.0 hours
TRT D: RLD at dose duration of 2.0 hours
UNT: Untreated control site (no product applied) corresponding to each treated site

Table AIV.2 Baseline-adjusted a-scale data for a subject

SUB	TRT	ARM	LOC.	SITE	BL	Hours after drug removal					
						0	2	4	6	19	24
1	A	R	1	UNT	-	-0.11	0.75	0.30	0.48	0.34	1.37
1	A	R	1	TRT	-	0.75	0.48	-1.19	-0.88	-0.79	0.19
1	B	R	2	UNT	-	1.20	1.08	0.67	1.17	0.96	1.69
1	B	R	2	TRT	-	-0.50	-0.67	-2.34	-0.91	-0.78	0.47
1	C	R	3	UNT	-	1.04	1.52	0.49	1.47	0.31	1.27
1	C	R	3	TRT	-	1.48	1.62	-0.36	0.46	-0.38	0.81
1	D	R	4	UNT	-	0.88	1.30	0.25	1.57	0.21	0.82
1	D	R	4	TRT	-	0.84	-0.44	-2.31	-0.40	-0.14	0.63
1	C	L	1	UNT	-	0.36	-0.06	-0.14	-0.38	-0.89	-0.13
1	C	L	1	TRT	-	-1.55	-1.58	-2.58	-2.18	-1.21	-0.52
1	B	L	2	UNT	-	-0.80	-0.36	-0.87	-0.38	-0.32	0.46
1	B	L	2	TRT	-	-2.98	-3.08	-3.35	-3.07	-1.19	-0.21
1	A	L	3	UNT	-	-0.66	0.04	-0.48	0.18	0.20	0.69
1	A	L	3	TRT	-	-0.24	-0.92	-2.25	-2.46	-1.85	-0.74
1	D	L	4	UNT	-	-0.71	-0.04	-0.49	0.11	0.06	0.94
1	D	L	4	TRT	-	-0.76	-2.09	-3.29	-3.66	-1.75	-0.84

Table AIV.3 Baseline-adjusted, untreated control site-corrected a-scale data and $AUEC_{(0\text{-}24)}$ data for a subject

SUB	TRT	ARM	LOC.	SITE	BL	Hours after drug removal						$AUEC_{(0\text{-}24)}$
						0	2	4	6	19	24	
1	A	R	1	TRT	-	0.86	-0.27	-1.49	-1.36	-1.13	-1.18	-25.98
1	B	R	2	TRT	-	-1.70	-1.75	-3.01	-2.08	-1.74	-1.22	-45.53
1	C	R	3	TRT	-	0.44	0.00	-0.85	-1.01	-0.69	-0.46	-16.20
1	D	R	4	TRT	-	-0.04	-1.74	-2.56	-1.97	-0.35	-0.29	-27.29
1	C	L	1	TRT	-	-1.91	-1.52	-2.44	-1.80	-0.32	-0.39	-27.19
1	B	L	2	TRT	-	-2.18	-2.72	-2.48	-2.69	-0.87	-0.67	-42.26
1	A	L	3	TRT	-	0.42	-0.96	-1.77	-2.64	-2.05	-1.43	-46.87
1	D	L	4	TRT	-	-0.05	-2.05	-2.80	-3.77	-1.81	-1.78	-58.77

Table AIV.4 Baseline-adjusted, untreated control site-corrected a-scale data of all 12 subjects

TEST PRODUCT											REFERENCE PRODUCT										
				Hours after drug removal											Hours after drug removal						
SUB	TRT	ARM	LOC	0	2	4	6	19	24		SUB	TRT	ARM	LOC	0	2	4	6	19	24	
1	C	R	3	0.44	0.00	-0.85	-1.01	-0.69	-0.46		1	D	R	4	-0.04	-1.74	-2.56	-1.97	-0.35	-0.29	
1	C	L	1	-1.91	-1.52	-2.44	-1.80	-0.32	-0.39		1	D	L	4	-0.05	-2.05	-2.80	-3.77	-1.81	-1.78	
2	C	R	3	-1.51	-3.29	-3.45	-4.11	-0.89	-1.26		2	D	R	4	-0.23	-1.58	-2.53	-2.53	0.00	-0.49	
2	C	L	1	0.23	-1.09	-0.94	-2.15	-2.05	-0.66		2	D	L	4	-2.30	-2.88	-2.15	-3.05	2.09	0.27	
3	C	L	3	-1.29	-1.75	-0.98	-0.90	-3.06	-1.05		3	D	R	1	1.25	-0.10	-1.99	-1.52	0.24	-1.24	
3	C	R	2	0.02	-1.43	-2.24	-1.16	-1.58	-1.72		3	D	L	4	-0.04	-0.26	-1.30	-1.23	-0.77	-1.07	
4	C	R	1	-0.02	-0.19	-0.52	-1.00	-0.43	-0.50		4	D	R	4	-0.43	-0.34	-1.50	-1.80	-0.74	-0.96	
4	C	L	3	-0.12	0.15	-0.29	-0.06	-0.07	0.12		4	D	L	2	-0.47	-0.22	-0.49	-0.83	-0.89	-0.82	
5	C	L	3	-0.36	-0.01	-0.19	-0.06	-0.72	-0.28		5	D	L	2	-0.71	-1.77	-1.62	-2.62	-0.76	-0.60	
5	C	R	1	-0.02	-0.63	-1.13	-0.90	-0.88	-0.03		5	D	R	3	0.46	-1.23	-1.23	-1.61	-1.70	-0.47	
6	C	R	4	0.60	0.32	0.32	0.30	-1.09	-1.53		6	D	R	1	-0.11	0.20	1.35	0.86	-0.77	-1.00	
6	C	L	3	-1.08	-0.45	-0.98	-0.83	-1.18	-0.07		6	D	L	4	-0.96	-1.07	-0.52	-1.17	-2.33	-1.52	
7	C	R	4	-0.28	0.25	-0.34	-0.64	-0.64	-0.41		7	D	R	2	-0.22	-0.30	-0.42	-0.18	-0.74	-1.00	
7	C	L	1	0.67	0.74	0.72	1.03	0.33	-0.11		7	D	L	4	-0.51	0.03	-0.76	-0.12	-0.42	-1.24	
8	C	R	4	-0.40	0.49	0.46	0.00	-0.35	0.78		8	D	R	2	0.51	0.30	0.92	0.63	0.56	0.34	
8	C	L	3	0.30	0.05	0.07	0.19	-0.05	-0.28		8	D	L	1	-0.44	0.08	-0.16	-0.95	-2.00	-1.49	
9	C	R	1	-0.71	-1.13	-1.94	-2.40	-1.70	-1.41		9	D	R	4	-0.40	-1.15	-2.25	-2.57	-1.20	-1.55	
9	C	L	3	-0.34	-0.52	-1.48	-1.41	-0.31	-1.10		9	D	L	2	-1.16	-1.05	-1.90	-1.80	-1.06	-1.42	
10	C	R	1	-0.49	-0.43	-0.63	-0.10	-0.50	-1.10		10	D	L	3	0.28	-0.31	-1.16	-1.40	-0.64	-0.57	
10	C	L	3	0.10	-0.66	-0.44	-0.68	-0.34	-0.86		10	D	R	1	-0.14	-0.05	-0.24	-0.63	-0.41	-1.09	
11	C	L	2	-0.58	-0.93	-1.60	-2.29	-0.24	-0.54		11	D	R	1	-0.46	-0.82	-1.10	-2.15	-0.47	-0.59	
11	C	R	3	0.12	-1.67	-1.71	-2.34	0.15	-1.28		11	D	L	4	-0.15	-1.45	-1.66	-1.61	-1.14	0.55	
12	C	L	3	0.05	-0.08	-0.18	-0.36	-1.28	-0.46		12	D	R	1	-0.25	-0.76	-1.35	-2.29	-1.23	-0.99	
12	C	R	3	-0.60	0.15	0.19	-0.42	-0.40	-0.32		12	D	L	4	1.89	0.73	2.07	0.82	-0.59	0.70	
MEAN				-0.30	-0.57	-0.86	-0.96	-0.76	-0.62						-0.19	-0.74	-1.08	-1.40	-0.71	-0.76	
SD				0.65	0.91	1.01	1.12	0.76	0.59						0.79	0.87	1.23	1.2	0.9	0.68	
SE				0.13	0.19	0.21	0.23	0.16	0.12						0.16	0.18	0.25	0.25	0.18	0.14	
%CV				217	161	118	117	100	96						405	117	116	86	126	89	

Table AIV.5 $AUEC_{(0\text{-}24)}$ data for the right arm, the left arm, and the two arm average at dose durations equal to D_1 and D_2, and the ratio of average AUEC at D_2/average AUEC at D_1 of all 12 subjects

$AUEC_{(0\text{-}24)}$ at D_1				$AUEC_{(0\text{-}24)}$ at D_2				AUEC at D_2/AUEC at D_1*
SUB	ARM	AUEC	AUEC (AVERAGE)	SUB	ARM	AUEC	AUEC (AVERAGE)	
1	R	-25.98	-36.42	1	R	-45.53	-43.90	1.21
1	L	-46.87		1	L	-42.26		
2	R	-62.43	-46.09	2	R	-69.72	-59.96	1.33
2	L	-27.76		2	L	-50.20		
3	R	-22.53	-28.41	3	R	-31.87	-64.04	2.25
3	L	-34.29		3	L	-96.21		
4	R	-7.49	-11.70	4	R	-27.48	-23.30	1.99
4	L	-15.91		4	L	-19.12		
5	L	-16.59	-17.38	5	L	-25.01	-16.58	0.95
5	R	-18.14		5	R	-8.15		
6	R	-8.24	-10.44	6	R	-27.36	-9.33	0.89
6	L	-12.64		6	L	8.70		
7	R	-10.89	-13.38	7	L	-20.44	-23.68	1.77
7	L	-15.83		7	R	-26.92		
8	L	7.08	4.69	8	R	-26.16	-21.02	-4.48
8	R	2.31		8	L	-15.88		
9	L	-34.22	-13.82	9	R	-33.60	-21.39	1.55
9	R	6.68		9	L	-8.97		
10	L	-4.10	3.06	10	R	-62.60	-43.79	-14.29
10	R	10.23		10	L	-34.97		
11	R	-33.30	-37.30	11	R	-57.00	-52.20	1.40
11	L	-41.30		11	L	-47.40		
12	R	-0.55	-21.08	12	R	-29.24	-28.22	1.34
12	L	-41.57		12	L	-27.20		

*Highlighted cells indicate AUEC ratio ≥ 1.25.

Table AIV.6 $AUEC_{(0-24)}$ data for right and left arms, the two arm average data for test and reference products of all 12 subjects at a dose duration of 2.0 hours

$AUEC_{(0-24)}$ of TEST PRODUCT					$AUEC_{(0-24)}$ of REFERENCE PRODUCT				
SUB	ARM	LOC	AUEC	AUEC* (AVERAGE)	SUB	ARM	LOC	AUEC	AUEC* (AVERAGE)
1	R	3	-16.20	-21.69	1	R	4	-27.29	-43.03
1	L	1	-27.19		1	L	4	-58.77	
2	L	3	-56.98	-48.52	2	R	4	-28.65	-22.20
2	R	1	-40.06		2	L	4	-15.75	
3	L	3	-43.63	-38.99	3	R	1	-15.27	-18.65
3	R	2	-34.36		3	L	4	-22.03	
4	R	1	-14.06	-7.62	4	R	4	-26.67	-22.42
4	L	3	-1.18		4	L	2	-18.18	
5	L	3	-8.39	-13.34	5	L	2	-35.48	-34.25
5	R	1	-18.29		5	R	3	-33.01	
6	R	4	-9.51	-15.23	6	R	1	0.01	-18.83
6	L	3	-20.96		6	L	4	-37.68	
7	R	4	-12.05	0.98	7	R	2	-12.17	-10.96
7	L	1	14.01		7	L	4	-9.75	
8	R	4	0.30	0.56	8	R	2	13.67	-7.94
8	L	3	0.81		8	L	1	-29.45	
9	R	1	-43.68	-32.05	9	R	4	-41.15	-37.40
9	L	3	-20.42		9	L	2	-33.65	
10	R	1	-10.61	-11.51	10	L	3	-20.35	-16.10
10	L	3	-12.41		10	R	1	-11.86	
11	L	2	-26.33	-26.18	11	R	1	-26.13	-26.73
11	R	3	-26.04		11	L	4	-27.33	
12	L	3	-15.77	-11.62	12	R	1	-35.19	-12.56
12	R	3	-7.47		12	L	4	10.08	
MEAN			-18.77	-18.77				-22.59	-22.59
SD			16.45	15.28				16.14	10.92
SE			3.36	3.12				3.30	2.23
%CV			88	81				71	48

*Highlighted cells show AUEC data of seven subjects whose AUEC ratios (see Table AIV.5) were ≥ 1.25, i.e., evaluable subjects. These AUEC data were used in the calculation of the 90% confidence interval in Appendix V.

APPENDIX V

LOCKE'S METHOD: FORMULAE AND A WORKED EXAMPLE

The calculation of the 90% confidence interval for the 'pivotal' bioequivalence data set of Table AIV.6 is given below. The data used to calculate the confidence interval are the average AUEC values of 'detectors' (evaluable subjects) only.

Table AV.1 Average AUEC values of subjects in the 'pivotal' study meeting the dose duration-response criterion of Section V(H)(1)(c)

Subject	$AUEC_{(0\text{-}24)}$ Test Product (Average)	$AUEC_{(0\text{-}24)}$ Reference Product (Average)
2	-48.52	-22.20
3	-38.99	-18.65
4	-7.62	-22.42
7	0.98	-10.96
9	-32.05	-37.40
11	-26.18	-26.73
12	-11.62	-12.56

The calculation of the confidence interval is facilitated by the calculation of the following intermediate quantities:

$$\bar{X}_T = \frac{1}{n}\sum_{i=1}^{n} X_{Ti} \qquad \bar{X}_R = \frac{1}{n}\sum_{i=1}^{n} X_{Ri}$$

where n is the number of evaluable subjects, seven (7) in this example.

$$\hat{\sigma}_{TT} = \frac{\sum_{i=1}^{n}(X_{Ti} - \bar{X}_T)^2}{n-1} \qquad \hat{\sigma}_{RR} = \frac{\sum_{i=1}^{n}(X_{Ri} - \bar{X}_R)^2}{n-1}$$

$$\hat{\sigma}_{TR} = \frac{\sum_{i=1}^{n}(X_{Ti} - \bar{X}_T)(X_{Ri} - \bar{X}_R)}{n-1}$$

These are the sample means, sample variances, and sample covariance for the individual evaluable subject average AUEC data. For the example, these are

$$\bar{X}_T = -23.43 \quad \bar{X}_R = -21.56 \quad \hat{\sigma}_{TT} = 323.13 \quad \hat{\sigma}_{RR} = 80.10 \quad \hat{\sigma}_{TR} = 78.83$$

Define t as the 95th percentile of the t-distribution for n-1 degrees of freedom. For example, for n=7, t (6 degrees of freedom) is 1.9432. Now define

$$G = \frac{t^2 \, \hat{\sigma}_{RR}}{n \, \bar{X}_R^{\,2}}$$

G < 1 is required to have a proper confidence interval. If G ≥ 1, the study does not meet the *in vivo* bioequivalence requirements. In the example, G = .0930.

Under the assumption that G < 1, calculate

$$K = \left(\frac{\bar{X}_T}{\bar{X}_R}\right)^2 + \frac{\hat{\sigma}_{TT}}{\hat{\sigma}_{RR}}(1 - G) + \frac{\hat{\sigma}_{TR}}{\hat{\sigma}_{RR}}\left(G\frac{\hat{\sigma}_{TR}}{\hat{\sigma}_{RR}} - 2\frac{\bar{X}_T}{\bar{X}_R}\right)$$

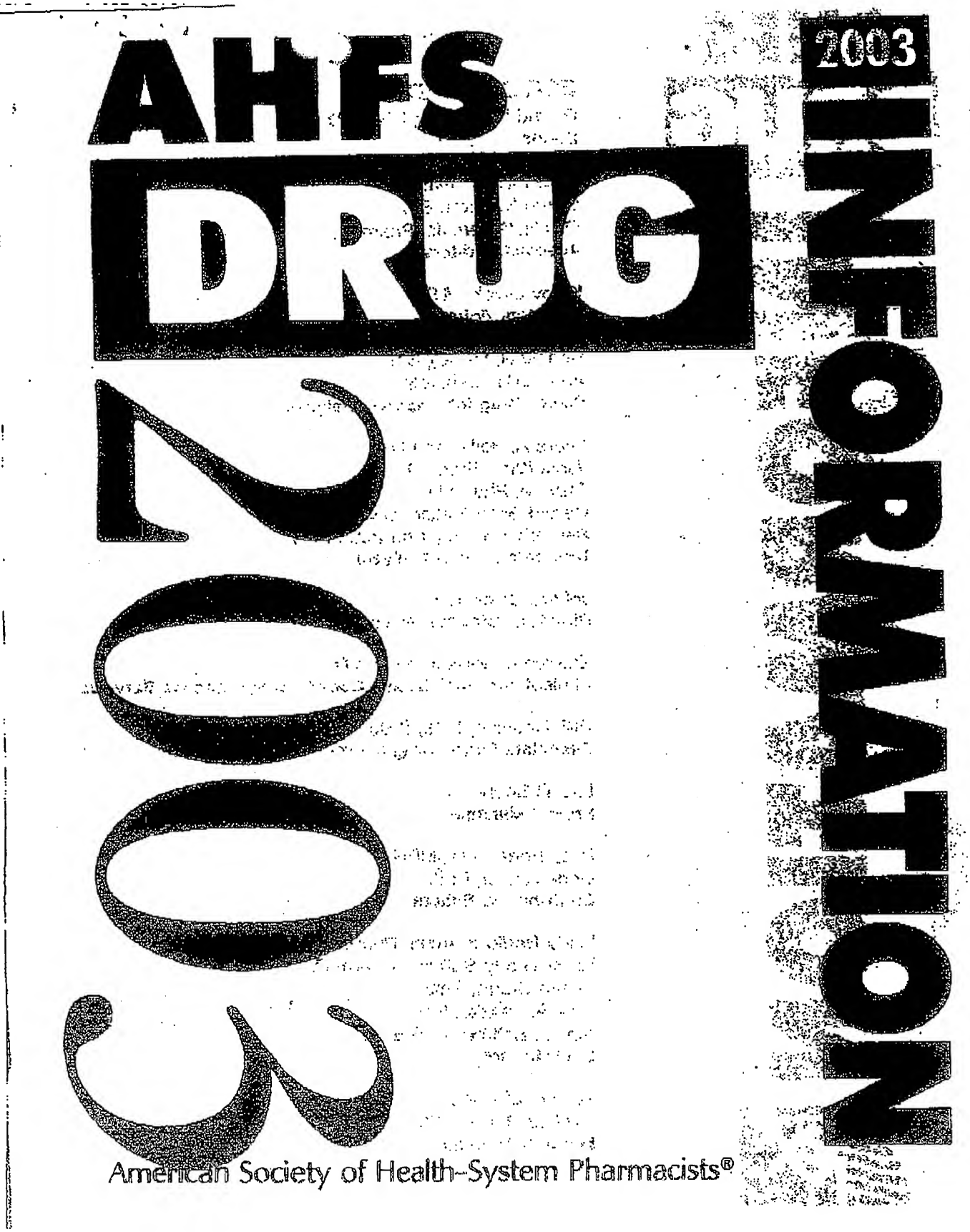
In the example, K = 2.791.

The confidence interval limits may now be calculated:

$$\frac{\left(\frac{\bar{X}_T}{\bar{X}_R} - G\frac{\hat{\sigma}_{TR}}{\hat{\sigma}_{RR}}\right) \mp \frac{t}{\bar{X}_R}\sqrt{\frac{\hat{\sigma}_{RR}}{n}K}}{1 - G}$$

In the example, 90% confidence interval limits are 53.6% and 165.9%, based on the data of seven evaluable subjects.

EXHIBIT C


AHFS
DRUG
2003
INFORMATION
2003
American Society of Health-System Pharmacists®

Printed in the United States of America.

LIBRARY OF CONGRESS CATALOG CARD NUMBER 59-7620

INTERNATIONAL STANDARD BOOK NUMBER (ISBN): 1-58528-039-9

INTERNATIONAL STANDARD SERIAL NUMBER (ISSN): 8756-6028

For Ordering Information

Write
American Society of Health-System Pharmacists
Customer Service Department
7272 Wisconsin Avenue
Bethesda, MD 20814 USA

Phone
301-657-4383

Fax
800-665-ASHP

Web
www.ahfsdruginformation.com

Please mention Order Code 718 when contacting us.
Payments to ASHP are not deductible as charitable contributions for federal income tax purposes. However, they may be deductible under other provisions of the Internal Revenue Code.

Acinetobacter, *Citrobacter*, *Enterobacter*, *Proteus*, *Serratia*, and streptococci in vitro. *Candida albicans* may be inhibited by silver sulfadiazine concentrations of 50–100 µg/mL, and *Herpesvirus hominis* may be inhibited by 10 µg/mL. In higher concentrations, the drug inhibits *Clostridium perfringens*.

Pharmacokinetics

Silver sulfadiazine itself does not appear to be absorbed. When in contact with body tissues and fluids, silver sulfadiazine slowly reacts with sodium chloride, sulfhydryl groups, and protein, resulting in the release of sulfadiazine. Sulfadiazine may be systemically absorbed from the site of application, particularly when silver sulfadiazine is applied to second-degree burns. When the drug is applied to extensive burns, serum sulfadiazine concentrations of up to 12 mg/dL have been reported. In one study, patients who were treated with 5–10 g of silver sulfadiazine daily applied as a 1% cream were found to have blood sulfadiazine concentrations of 1–2 mg/dL. 100–200 mg of sulfadiazine was excreted in urine within 24 hours following application of the cream. When 5–15 g/kg of a cream containing 1% silver sulfadiazine was applied daily for 100 days to experimentally abraded areas on rabbits, an unidentified silver compound was deposited in renal tissue; however, concurrent impairment of renal function was not noted.

Chemistry and Stability

Chemistry

Silver sulfadiazine is a synthetic anti-infective agent produced by the reaction of silver nitrate with sulfadiazine. Silver sulfadiazine occurs as a white, fluffy powder and is practically insoluble in water. The commercially available cream contains silver sulfadiazine in micronized form.

Stability

Silver sulfadiazine cream should be stored at 15–30°C.

Silver sulfadiazine reacts with most heavy metals; this reaction may result in release of free silver and darkening of the cream. If this occurs, the cream should be discarded. When silver sulfadiazine is used in conjunction with topical proteolytic enzymes, the possibility that silver may inactivate the proteolytic enzymes should be considered; however, the manufacturer of Elase (no longer commercially available in the US) has stated that this did not occur with its product.

Preparations

Silver Sulfadiazine

Topical

Cream	1%*	SSD* (with cetyl alcohol, methylparaben, and propylene glycol), Par
		SSD AF* (with methylparaben and propylene glycol), Par
		Silvadene* (with methylparaben and propylene glycol), Monarch
		Thermazene* (with methylparaben and propylene glycol), Major, Par, Sherwood, Zenith Goldline

*available by nonprescription order

ANTI-INFLAMMATORY AGENTS 84:06

Topical Corticosteroids General Statement

Hydrocortisone or synthetic derivatives of hydrocortisone are used topically as anti-inflammatory agents.

Uses

Dermatoses

Topical corticosteroids are used for the symptomatic relief of inflammatory dermatoses. The cause of the ... should be determined and eliminated if possible; dermatoses are controlled, but not cured, by these drugs. Although systemic corticosteroids are more effective in most dermatologic inflammations, topical treatment is preferred in most responsive cases because it causes fewer adverse systemic effects.

Topical corticosteroids generally are most effective in the treatment of acute or chronic dermatoses such as seborrheic or atopic dermatitis, localized neurodermatitis, anogenital pruritus, psoriasis (particularly of the face and between skin folds), and the inflammatory phase of xerosis. Topical corticosteroids are effective in the late phase of allergic contact dermatitis or irritant dermatitis, but systemic corticosteroids are usually required to relieve the acute manifestations of these dermatoses.

Individual topical corticosteroid preparations vary in anti-inflammatory activity (as measured by vasoconstrictor assay) and in percutaneous penetration, but therapeutic efficacy of a particular drug can often be increased by increasing the concentration or by using occlusive dressing therapy. As with systemic use, some patients may respond better to one topical corticosteroid than to another. Topical corticosteroid preparations may be grouped according to relative anti-inflammatory activity, but activity may vary *considerably depending upon the vehicle, the site of application, disease, the individual patient, and whether or not an occlusive dressing is used.* (See Pharmacokinetics.) Approximate relative activity (based principally on vasoconstrictor assay and/or clinical effectiveness in psoriasis) of some topical corticosteroid preparations in decreasing order is as follows (preparations in each group are approximately equivalent):

Group I

Betamethasone dipropionate (Diprolene*) cream (optimized vehicle) or ointment (optimized vehicle) 0.05% (of betamethasone)
Betamethasone dipropionate (Diprolene* AF) cream 0.05% (of betamethasone)
Clobetasol propionate (Temovate*, Clus*) cream, foam, or ointment 0.05%
Diflorasone diacetate (Psorcon*) ointment (optimized vehicle) 0.05%

Group II

Amcinonide (Cyclocort*) ointment 0.1%
Betamethasone dipropionate (Diprosone*) ointment 0.05% (of betamethasone)
Desoximetasone (Topicort*) cream or ointment 0.25%
Desoximetasone (Topicort*) gel 0.05%
Diflorasone diacetate (Florone*, Maxiflor*) ointment 0.05%
Fluocinonide (Lidex*) cream or ointment 0.05%
Fluocinonide gel 0.05%
Halcinonide (Halog*) cream 0.1%

Group III

Betamethasone benzoate gel 0.025%
Betamethasone dipropionate (Diprosone*) cream 0.05% (of betamethasone)
Betamethasone valerate (Valisone*) ointment 0.1% (of betamethasone)
Diflorasone diacetate (Florone*, Maxiflor*) cream 0.05%
Mometasone furoate (Elocon*) ointment 0.1%
Triamcinolone acetonide (Aristocort*) cream 0.5%

Group IV

Desoximetasone (Topicort* LP) cream 0.05%
Fluocinolone acetonide (Synalar-HP*) cream 0.2%
Fluocinolone acetonide (Synalar*) ointment 0.025%
Flurandrenolide (Cordran*) ointment 0.05%
Triamcinolone acetonide (Aristocort*, Kenalog*) ointment 0.1%

Group V

Betamethasone benzoate cream 0.025%
Betamethasone dipropionate (Diprosone*) lotion 0.05% (of betamethasone)
Betamethasone valerate (Valisone*) cream 0.1% (of betamethasone)
Betamethasone valerate (Valisone*) lotion 0.1% (of betamethasone)
Fluocinolone acetonide (Synalar*) cream 0.025%
Flurandrenolide (Cordran*) cream 0.05%
Hydrocortisone butyrate (Locoid*) cream 0.1%
Hydrocortisone valerate (Westcort*) cream 0.2%
Prednicarbate (Dermatop* Emollient) cream 0.1%
Triamcinolone acetonide (Kenalog*) cream 0.1%
Triamcinolone acetonide (Kenalog*) lotion 0.1%

Group VI

Alclometasone dipropionate (Aclovate*) cream or ointment 0.05%
Desonide (Tridesilon*) cream 0.05%
Fluocinolone acetonide (Synalar*) solution 0.01%

the scalp and hairy areas of the trunk and extremities, is applied and rubbed thoroughly into the affected area twice daily. Following application of the lotion, the affected area should be protected (i.e., from washing, clothing, or rubbing) until the lotion has dried. Occlusive dressings may be used for severe or resistant dermatoses.

Chemistry and Stability

Chemistry

Amcinonide is a synthetic fluorinated corticosteroid. Amcinonide occurs as a white solid and is insoluble in water.

Stability

Amcinonide cream should be stored in well-closed containers at a temperature less than 40°C, preferably between 15–30°C; freezing should be avoided. Amcinonide lotion and ointment should be stored at 15–30°C; freezing of the lotion should be avoided.

For further information on chemistry, pharmacology, absorption, uses, cautions, methods of application, and use of occlusive dressings in therapy with amcinonide, see the Topical Corticosteroids General Statement 84:06.

Preparations

Amcinonide

Topical		
Cream	0.1%	Cyclocort® (with benzyl alcohol 2% and Aquatain® hydrophilic base), Fujisawa
Lotion	0.1%	Cyclocort® (with benzyl alcohol 1% v/w and Aquatain® hydrophilic base), Fujisawa
Ointment	0.1%	Cyclocort® (with benzyl alcohol and propylene glycol), Fujisawa

Betamethasone

Rubenisolone

■ Betamethasone is a synthetic fluorinated corticosteroid.

Uses

Betamethasone shares the actions of the other topical corticosteroids and is used for the relief of the inflammatory manifestations of corticosteroid-responsive dermatoses.

For systemic uses of betamethasone, see 68:04.

Dosage and Administration

Betamethasone dipropionate and valerate are applied topically; concentrations of the dipropionate and valerate preparations usually are expressed in terms of betamethasone. Concentration of betamethasone valerate foam is expressed in terms of betamethasone valerate. Topical preparations of the drugs usually are applied sparingly in thin films and are rubbed gently into the affected area 1–4 times daily; betamethasone dipropionate lotions, creams, and ointments are applied once or twice daily. Dosage of 0.05% gels or lotions in an optimized (augmented) vehicle (e.g., Diprolene® AF cream, Diprolene® lotion) should not exceed 50 g or 50 mL per week, respectively; duration of therapy with these preparations should not exceed 14 days. Dosage of 0.05% ointments or creams in an optimized (augmented) vehicle should not exceed 45 g per week. When betamethasone aerosols are applied, an area about the size of one patient's hand is sprayed for not more than 3 seconds from a distance of about 15 cm 3 or 4 times daily. Betamethasone *dipropionate* preparations and betamethasone *valerate* foam preparations should *not* be used with occlusive dressings and patients should be warned that treated areas of the skin should not be bandaged or otherwise covered or wrapped as to be occlusive, unless directed by a clinician. For application to the scalp, the can containing betamethasone valerate foam should be inverted and small amounts of the preparation placed on a saucer or other cool surface. The foam should not be dispensed directly to the hands since the foam will begin to melt immediately upon contact with warm skin. Small amounts of the preparation should be massaged gently into the scalp until the foam disappears and entire scalp area has been treated.

Cautions

Betamethasone shares the toxic potentials of other topical corticosteroids, and the usual precautions of corticosteroid therapy should be observed. (See Cautions in the Topical Corticosteroids General Statement 84:06.)

Betamethasone dipropionate gels, lotions, creams, and ointments, particularly those in optimized (augmented) vehicles, are some of the most potent topical corticosteroids currently available. Because of their potency, these preparations can suppress the hypothalamic-pituitary-adrenal (HPA) axis following topical application, and reversible HPA-axis suppression has occurred following topical dosages as low as 7 g, 7 mL, or 7 g of the 0.05% betamethasone dipropionate gel, lotion, or cream, respectively, in optimized (augmented) vehicles (3.5 mg of betamethasone) daily. Reversible HPA-axis suppression has also occurred following repeated topical dosages of 14 g of the 0.05% ointment in an optimized (augmented) vehicle (7 mg of betamethasone) daily in patients with psoriasis, and minimal suppression has occurred following 25 g of this ointment (1.75 mg of betamethasone) twice daily for 2–3 weeks in healthy individuals and in patients with psoriasis or eczema.

Pediatric Precautions

Lotrisone® cream is not recommended for use in the treatment of diaper dermatitis. Use of Diprolene® cream or ointment preparations in children younger than 12 years of age is not recommended, and the safety and efficacy of Diprolene® lotion in children younger than 12 years of age have not been established. In addition, the safety and efficacy of Luxiq® foam in pediatric patients have not been established. (See Cautions: Pediatric Precautions, in the Topical Corticosteroids General Statement 84:06.)

Chemistry and Stability

Chemistry

Betamethasone is a synthetic fluorinated corticosteroid. Betamethasone occurs as a white to practically white, crystalline powder and is insoluble in water and sparingly soluble in alcohol. Betamethasone currently is commercially available for topical use only as betamethasone dipropionate and valerate esters. Betamethasone dipropionate occurs as a white to off-white powder and is insoluble in water. Betamethasone valerate occurs as a white to practically white powder and is practically insoluble in water and soluble in alcohol.

Stability

Betamethasone preparations should be stored as directed by the manufacturer.

For further information on chemistry, pharmacology, absorption, uses, cautions, methods of application, and use of occlusive dressings in therapy with betamethasone, see the Topical Corticosteroids General Statement 84:06.

Preparations

Betamethasone Dipropionate

Topical		
Aerosol	60 µg (of betamethasone) per 3-second spray	Diprosone® Aerosol (with isopropyl alcohol 10% and hydrocarbon propellants), Schering
Cream	0.05% (of betamethasone)*	Alphatrex®, Savage
		Del-Beta®, Del-Ray
		Diprolene® AF (with propylene glycol in an optimized [augmented] vehicle), Schering
		Diprosone® (with propylene glycol), Schering
		Maxivate®, Westwood-Squibb
Gel	0.05% (of betamethasone)	Diprolene® (with propylene glycol in an optimized [augmented] vehicle), Schering
Lotion	0.05% (of betamethasone)*	Alphatrex® (with isopropyl alcohol), Savage
		Del-Beta®, Del-Ray
		Diprolene® Lotion (with isopropyl alcohol 30% and propylene glycol in an optimized [augmented] vehicle), Schering
		Diprosone® (with isopropyl alcohol 46.8%), Schering
		Maxivate® (with isopropyl alcohol), Westwood-Squibb
Ointment	0.05% (of betamethasone)*	Alphatrex®, Savage
		Betamethasone Dipropionate Augmented Ointment, Alpharma, Wyeth
		Diprolene® (with propylene glycol in an optimized [augmented] vehicle), Schering

Lotion	0.05%	DesOwen® (with xanthan and propylene glycol), Galderma
Ointment	0.05%*	DesOwen®, Galderma Tridesilon®, Bayer, Clay-Park

*available by nonproprietary name

Desoximetasone

Desoxymetasone

■ Desoximetasone is a synthetic fluorinated corticosteroid.

Uses

Desoximetasone shares the actions of the other topical corticosteroids and is used for the relief of the inflammatory manifestations of corticosteroid-responsive dermatoses.

Dosage and Administration

Topical desoximetasone is applied sparingly in a thin film and rubbed gently into the affected area twice daily.

Chemistry and Stability

■ Chemistry

Desoximetasone is a synthetic fluorinated corticosteroid. The drug occurs as a white crystalline powder and is very slightly soluble in water and sparingly soluble in alcohol.

■ Stability

Desoximetasone preparations should be stored in well-closed containers at 15–30°C.

For further information on chemistry, pharmacology, absorption, uses, cautions, methods of application, and use of occlusive dressings in therapy with desoximetasone, see the Topical Corticosteroids General Statement 84:06.

Preparations

Desoximetasone

Topical		
Cream	0.05%	Desoximetasone Cream, Major, Taro, Zenith Goldline
		Topicort® LP, Medicis
	0.25%*	Topicort®, Medicis
Gel	0.05%	Desoximetasone Gel, Taro
		Topicort® (with SD alcohol 40 20% w/w), Medicis
Ointment	0.25%	Topicort® (with propylene glycol), Medicis
		Desoximetasone Ointment, Fougera, Taro

*available by nonproprietary name

Diflorasone Diacetate

■ Diflorasone diacetate is a synthetic fluorinated corticosteroid.

Uses

Diflorasone diacetate shares the actions of the other topical corticosteroids and is used for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Dosage and Administration

Topical diflorasone diacetate cream is applied sparingly in a thin film and rubbed gently into the affected area 2–4 times daily; the emollient cream preparation (Florone E®) and the ointments, including the enhanced-potency preparation (Florone®), are applied 1–3 times daily. Occlusive dressings may be used for severe or resistant dermatoses. Although the manufacturer of Psorcon® states that occlusive dressings also may be used with this enhanced-potency preparation, some clinicians recommend that occlusion generally be avoided with this preparation until additional safety data are available.

Chemistry and Stability

■ Chemistry

Diflorasone diacetate is a synthetic fluorinated corticosteroid. The drug occurs as a white to buff-colored powder and is insoluble in water.

■ Stability

Diflorasone diacetate preparations should be stored in well-closed containers at 15–30°C.

For further information on chemistry, pharmacology, absorption, uses, cautions, methods of application, and use of occlusive dressings in therapy with diflorasone diacetate, see the Topical Corticosteroids General Statement 84:06.

Preparations

Diflorasone Diacetate

Topical		
Cream	0.05%	Diflorasone Diacetate Cream, Fougera, Taro
		Florone® (with propylene glycol), Dermik
		Florone E® Emollient Cream (with propylene glycol; in a hydrophilic cream base), Dermik
		Maxiflor® (with propylene glycol), Allergan
		Psorcon® (with propylene glycol), Dermik
		Psorcon E® Emollient Cream (with propylene glycol; in a hydrophilic cream base), Dermik
Ointment	0.05%	Diflorasone Diacetate Ointment, Fougera, Taro
		Florone®, Dermik
		Maxiflor®, Allergan
		Psorcon® (with propylene glycol), Dermik

Fluocinolone Acetonide
Fluocinonide

■ Fluocinolone acetonide and fluocinonide are synthetic fluorinated corticosteroids.

Uses

Fluocinolone acetonide and fluocinonide share the actions of the other topical corticosteroids and are used for the relief of the inflammatory manifestations of corticosteroid-responsive dermatoses.

Dosage and Administration

Fluocinolone acetonide shampoo should be prepared by a pharmacist at the time of dispensing the shampoo; contents of the 12-mg capsule should be mixed with the shampoo base supplied by the manufacturer. The extemporaneously prepared shampoo is stable for 3 months from the time of compounding. The extemporaneously prepared shampoo must be shaken well prior to administration.

Topical preparations of fluocinolone acetonide are applied 2–4 times daily. Fluocinonide preparations are applied topically 3 or 4 times daily. Preparations of the drugs are applied sparingly in thin films and are rubbed gently into the affected area. Occlusive dressings may be used for severe or resistant dermatoses.

Chemistry and Stability

■ **Chemistry**

Fluocinolone acetonide and fluocinonide are synthetic fluorinated corticosteroids. Fluocinolone acetonide occurs as an anhydrous or dihydrate, white or practically white, crystalline powder and is insoluble in water, soluble in alcohol, and sparingly soluble in propylene glycol. Fluocinonide, the 21-acetate ester of fluocinolone acetonide, occurs as a white to cream-colored, crystalline powder having not more than a slight odor and is practically insoluble in water and slightly soluble in alcohol.

■ **Stability**

Fluocinolone acetonide and fluocinonide preparations should be stored in tight containers at a temperature less than 40°C, preferably between 15–30°C; freezing should be avoided.

The extemporaneously prepared shampoo is stable for 3 months from time of compounding. (See Dosage and Administration.)

For further information on chemistry, pharmacology, absorption, uses, cautions, methods of application, and use of occlusive dressings in therapy with fluocinolone acetonide and fluocinonide, see the Topical Corticosteroids General Statement 84:06.

Preparations

Fluocinolone Acetonide

Topical

Cream	0.01%*	Synalar® (with parabens and propylene glycol), Medicis
	0.025%	Synalar® Emollient Cream, Medicis
For shampoo	0.01%	Capex® Shampoo, Galderma; FS® Shampoo (available as fluocinolone acetonide 12 mg capsule and shampoo base with parabens and propylene glycol to prepare 180 mL of shampoo), Hill
Oil	0.01%	Derma-Smoothe/FS® (with isopropyl alcohol), Hill
Ointment	0.025%	Fluocinolone Acetonide Ointment, Fougera, Taro, Major, Mova, Zenith Goldline
		Synalar®, Medicis
Solution	0.01%*	Fluonid® (with propylene glycol), Allergan
		Synalar® (with propylene glycol), Medicis

*available by nonproprietary name

Fluocinonide

Topical

Cream	0.05%*	Fluocinonide E Emollient Cream, Alphamed, Major, Taro, Teva, Zenith Goldline
		Lidex® (with propylene glycol), Medicis
		Lidex®-E Emollient Cream® (with propylene glycol), Medicis
Gel	0.05%*	Fluocinonide Gel, Fougera, Taro, Teva
		Lidex® Gel (with propylene glycol), Medicis
Ointment	0.05%*	Lidex® (with propylene glycol), Medicis
Solution	0.05%*	Lidex® (with alcohol 35% and propylene glycol), Medicis

*available by nonproprietary name

Flurandrenolide

Flurandrenolone Acetonide

■ Flurandrenolide is a synthetic fluorinated corticosteroid.

Uses

Flurandrenolide shares the actions of the other topical corticosteroids and is used for the relief of the inflammatory manifestations of corticosteroid-responsive dermatoses.

Dosage and Administration

Topical preparations of flurandrenolide are applied sparingly in thin films and are rubbed gently into the affected area 2 or 3 times daily. Occlusive dressings may be used for severe or resistant dermatoses. The topical dressing (tape) is generally applied as an occlusive dressing to clean, dry affected areas every 12 hours.

Chemistry and Stability

■ **Chemistry**

Flurandrenolide is a synthetic fluorinated corticosteroid. The drug occurs as a white to tiff-white, fluffy, crystalline powder and is practically insoluble in water and sparingly soluble in alcohol.

■ **Stability**

Flurandrenolide cream, lotion, and ointment should be protected from light and stored in tight containers at a temperature less than 40°C, preferably between 15–30°C; freezing should be avoided. Flurandrenolide tape should be stored at 15–30°C.

For further information on chemistry, pharmacology, absorption, uses, cautions, methods of application, and use of occlusive dressings in therapy with flurandrenolide, see the Topical Corticosteroids General Statement 84:06.

Preparations

Flurandrenolide

Topical

Cream	0.025%	Cordran® SP (with propylene glycol), Odan/Sein
	0.05%	Cordran® SP (with propylene glycol), Odan/Sein
Dressing	4 µg/cm²	Cordran® Tape, Odan/Sein
Lotion	0.05%	Cordran® (with benzyl alcohol), Odan/Sein
Ointment	0.025%	Cordran®, Odan/Sein
	0.05%	Cordran®, Odan/Sein

Halcinonide

■ Halcinonide is a synthetic fluorinated corticosteroid.

Uses

Halcinonide shares the actions of the other topical corticosteroids and is used for the relief of the inflammatory manifestations of corticosteroid-responsive dermatoses.

Dosage and Administration

Topical preparations of halcinonide are applied sparingly in thin films and are rubbed gently into the affected area 2 or 3 times daily. Occlusive dressings may be used for severe or resistant dermatoses.

Chemistry and Stability

■ **Chemistry**

Halcinonide, a synthetic fluorinated corticosteroid, occurs as a white, crystalline powder and is insoluble in water and slightly soluble in alcohol.

■ **Stability**

Halog®-E 0.1% cream should be stored in well-closed containers at room temperature; freezing or refrigeration should be avoided. Halog® creams and

Exhibit 3

U.S. Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Drug Details

Drug Name(s)	VANOS (Brand Name Drug)
FDA Application No.	(NDA) 021758
Active Ingredient(s)	FLUOCINONIDE
Company	MEDICIS

- There are no Therapeutic Equivalents
- Approval History and Related Documents
- Label Information

Products on Application (NDA) #021758

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	RLD	TE Code
VANOS	FLUOCINONIDE	0.1%	CREAM; TOPICAL	Prescription	Yes	None

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

Exhibit 4

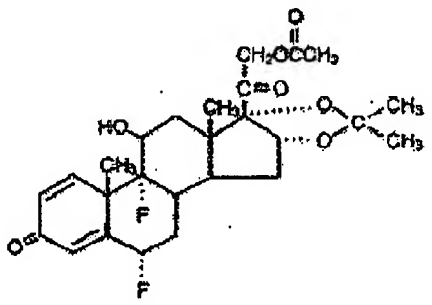
VANOS (fluocinonide) Cream, 0.1%
Rx Only

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

DESCRIPTION

VANOS (fluocinonide) Cream, 0.1% contains fluocinonide, a synthetic corticosteroid for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Fluocinonide has the chemical name 6 alpha, 9 alpha-difluoro-11 beta, 21-dihydroxy-16 alpha, 17 alpha-isopropylidenedioxypregna-1, 4-diene-3,20-dione 21-acetate. Its chemical formula is $C_{26}H_{32}F_2O_7$ and it has a molecular weight of 494.58.

It has the following chemical structure:



Fluocinonide is an almost odorless white to creamy white crystalline powder. It is practically insoluble in water and slightly soluble in ethanol.

Each gram of VANOS Cream contains 1 mg micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate NF, purified water USP, carbopol 980 NF, diisopropanolamine, and citric acid USP.

CLINICAL PHARMACOLOGY

The exact mechanism of action of topical corticosteroids, such as fluocinonide, in the treatment of psoriasis is not known. However, topical corticosteroids are thought to be effective primarily because of their anti-inflammatory, anti-pruritic, and vasoconstrictive

with VANOS Cream for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA-axis suppression.

If HPA-axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Application of VANOS Cream, 0.1% twice daily for 14 days in 18 adult patients with plaque-type psoriasis (10-50% BSA, mean 19.6% BSA) showed demonstrable HPA axis suppression in 2 patients (11%).

HPA axis suppression has not been evaluated in psoriasis patients who are less than 18 years old. Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See **PRECAUTIONS – Pediatric Use.)**

If irritation develops, VANOS Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of VANOS Cream should be discontinued until the infection has been adequately controlled.

VANOS Cream should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face, groin, or axillae.

Information for the Patient: Patients using VANOS Cream should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or unintended effects:

1. VANOS Cream is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. VANOS Cream should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped, so as to be occlusive unless directed by the physician.

actions. The mechanism of the anti-inflammatory activity of topical corticosteroids, in general, is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachadonic acid. Arachadonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Vasoconstrictor studies performed with VANOS Cream, 0.1% in healthy subjects indicate that it is in the super-high range of potency as compared with other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.

Application of VANOS Cream, 0.1% twice daily for 14 days in 18 adult patients with plaque-type psoriasis (10-50% BSA, mean 19.6% BSA) showed demonstrable HPA axis suppression in 2 patients (with 12% and 25% BSA) where the criterion for HPA axis suppression is a serum cortisol level of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation with cosyntropin ($ACTH_{1-24}$).

Treatment of patients with VANOS Cream for more than 2 weeks at a time is not recommended, and only small areas should be treated at any one time due to the increased risk of HPA-axis suppression (See **PRECAUTIONS**).

HPA axis suppression has not been evaluated in psoriasis patients who are less than 18 years of age.

CLINICAL STUDIES

A double masked, vehicle controlled, randomized study of VANOS Cream was conducted in patients with plaque-type psoriasis. Patients with 2% to 10% body surface area involvement at baseline applied either VANOS Cream or Vehicle Cream to all affected areas either once daily (*qd*) or twice daily (*bid*) for 14 consecutive days. The primary measure of efficacy was the proportion of patients whose psoriasis lesions cleared or almost cleared at the end of treatment. The results are presented in the table below as patients cleared or almost cleared at Week 2 with once or twice daily application of VANOS Cream.

4. Patients should report to their physician any signs of local adverse reactions.

5. Other corticosteroid-containing products should not be used with VANOS Cream without first talking to the physician.

6. If no improvement is seen in 2 weeks, the patient should be instructed to contact a physician. The safety of the use of VANOS Cream for longer than 2 weeks has not been established.

Laboratory Tests: The cosyntropin ($ACTH_{1-24}$) stimulation test may be helpful in evaluating patients for HPA axis suppression.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of fluocinonide.

Fluocinonide revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames test and an *in vitro* chromosomal aberration assay in human lymphocytes). However, fluocinonide was positive for clastogenic potential when tested in the in vivo mouse micronucleus assay.

Pregnancy Category C: Teratogenic Effects: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

There are no adequate and well-controlled studies in pregnant women. Therefore, VANOS Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Use in patients under 18 years of age is not recommended. Safety and effectiveness in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA-axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA-axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to cosyntropin ($ACTH_{1-24}$) stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use: Clinical studies of VANOS Cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious.

ADVERSE REACTIONS

In clinical trials, a total of 443 patients with atopic dermatitis or plaque-type psoriasis were treated once daily or twice daily with VANOS Cream for 2 weeks. The most commonly observed adverse events in these clinical trials were as follows:

Adverse Event	VANOS Cream, *once daily* (n=216)	VANOS Cream, *twice daily* (n=227)	Vehicle Cream, *once or twice daily* (n=211)
Headache	8/216 (3.7%)	9/227 (4.0%)	6/211 (2.8%)
Application Site Burning	5/216 (2.3%)	4/227 (1.8%)	14/211 (6.6%)
Nasopharyngitis	2/216 (0.9%)	3/227 (1.3%)	3/211 (1.4%)
Nasal Congestion	3/216 (1.4%)	1/227 (0.4%)	0
Unspecified Application Site Reaction	1/216 (0.4%)	1/227 (0.4%)	3/211 (1.4%)

No other adverse events were reported by more than 1 subject receiving active treatment. The incidence of all adverse events was similar between the active treatment groups and the vehicle control groups.

The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

Systemic absorption of topical corticosteroids has produced hypothalamic-pituitary-adrenal (HPA) axis suppression manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

OVERDOSAGE

Topically applied VANOS Cream can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Apply a thin layer of VANOS Cream once or twice daily to the affected skin areas, as directed by your physician. Twice daily application has been shown to be more effective in achieving treatment success after 2 weeks of treatment (see **CLINICAL STUDIES**).

Treatment with VANOS Cream should be limited to 2 consecutive weeks, and amounts greater than 60 g/week should not be used.

Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

HOW SUPPLIED

VANOS (fluocinonide) Cream 0.1% is supplied in aluminum tubes as follows:

30 g (NDC 99207-523-30)
60 g (NDC 99207-525-60)

Store at controlled room temperature: 15° to 30°C (59° to 86°F).

Manufactured for:
MEDICIS, The Dermatology Company ®
Scottsdale, AZ 85258

Manufactured by:
Patheon, Inc.
Mississauga, Ontario
Canada L5N 7K9

Made in Canada

U.S. Patent 6,765,001

Prescribing information as of February, 2005.

ULIDEX CREAM 0.1% 1.5g CARTON
8/30/04

Vanos™
(fluocinonide) cream 0.1%

NDC 99207-525-02

MEDICIS

Vanos™
(fluocinonide) cream 0.1%

Sample—Not for Sale
Available in 30 and 60 g tubes

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE

Rx only

Manufactured for: MEDICIS,
The Dermatology Company
Scottsdale, AZ 85258
By: Patheon, Inc.
Mississauga, Ontario
Canada L5N 7K9
Made in Canada

U.S. Patent 6,765,001

Dosage: See package insert for dosage information.

Vanos™
(fluocinonide) cream 0.1%

NDC 99207-525-02

MEDICIS

Vanos™
(fluocinonide) cream 0.1%

Sample—Not for Sale
Available in 30 and 60 g tubes

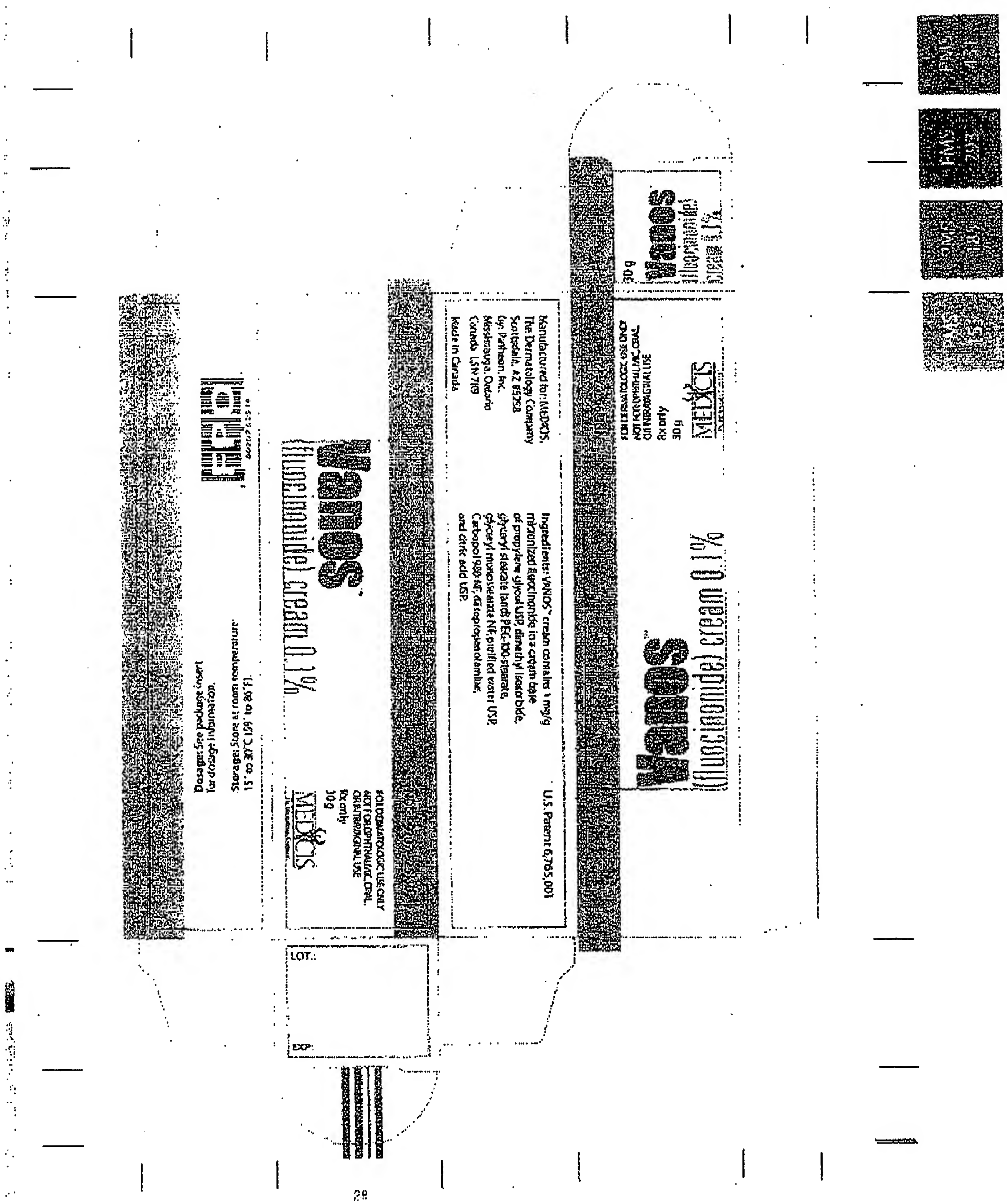
FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE

Rx only

Contains 20 sample tubes. Each tube contains 1.5 g.

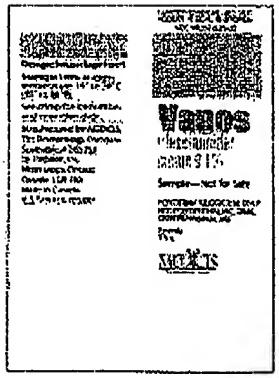
Ingredients: VANOS™ cream contains 1 mg/g micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, cetyl/oleyl monostearate NF, purified water USP, Carbopol 980 NF, diisopropanolamine and citric acid USP.

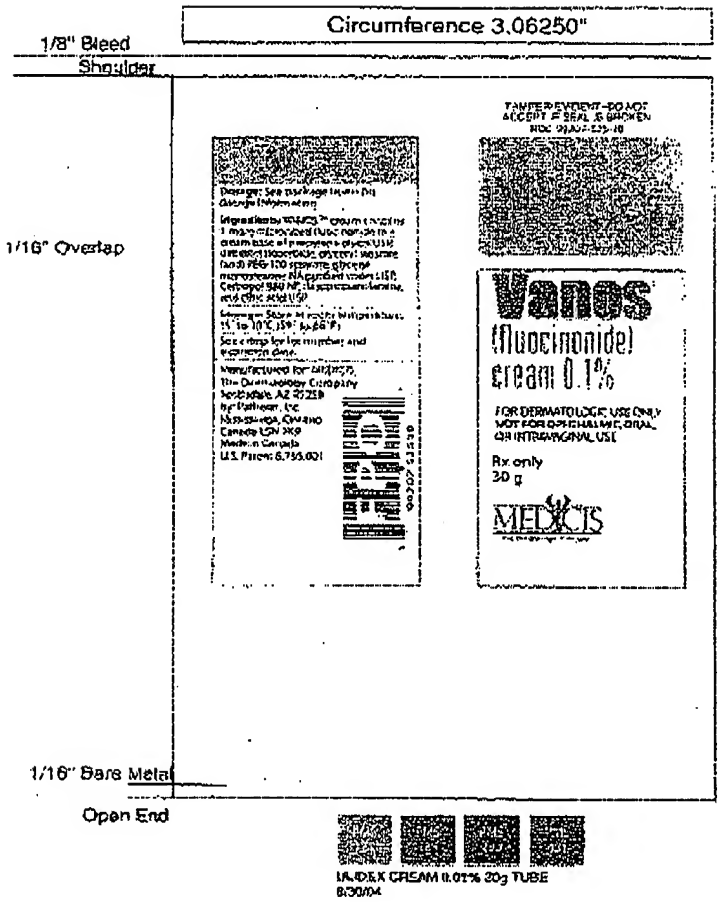
Storage: Store at room temperature: 15° to 30°C (59° to 86°F).

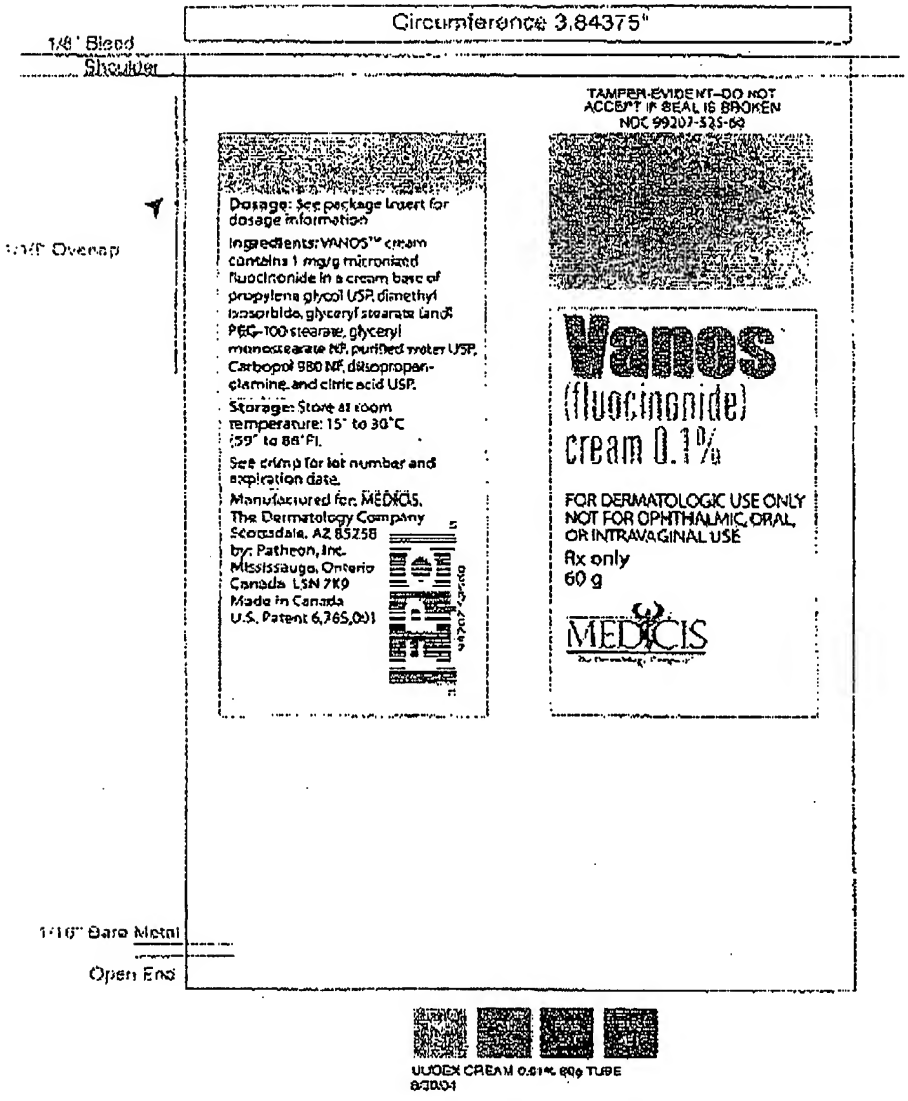


ULIDEX CREAM 0.1% 30g CARTON
8/30/04

Vanos
(fluocinonide) cream 0.1%
Dosage: See package insert for dosage information.
Storage: Store at room temperature; 15° to 30°C (59° to 86°F).
Vanos
(fluocinonide) cream 0.1%
LOT:
EXP:
Vanos
(fluocinonide) cream 0.1%
Manufactured for: MEDICIS, The Dermatology Company Scottsdale, AZ 85258
by: Patheon, Inc. Mississauga, Ontario Canada L5N 7K9
Made in Canada
Ingredients: VANOS™ cream contains 1 mg/g micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate NF, purified water USP, Carbopol 980 NF, diisopropanolamine, and citric acid USP.
U.S. Patent 6,765,001
60 g
Vanos
(fluocinonide) cream 0.1%
MEDICIS
ULIDEX CREAM 0.01% 60g CARTON
8/30/04


Vasos


Circumference 3.06250"
1/8" Bleed
Shoulder
1/16" Overlap
1/16" Bare Metal
Open End
Vanos
(fluocinonide)
cream 0.1%
FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC, ORAL
OR INTRAVAGINAL USE
Rx only
30 g
MEDICIS


Circumference 3.84375"
1/8" Bleed
Shoulder
1/16" Overlap
1/16" Bare Metal
Open End
TAMPER-EVIDENT–DO NOT ACCEPT IF SEAL IS BROKEN
NDC 99207-525-60
Dosage: See package insert for dosage information
Ingredients: VANOS™ cream contains 1 mg/g micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate and PEG-100 stearate, glyceryl monostearate NF, purified water USP, Carbopol 980 NF, diisopropanolamine, and citric acid USP.
Storage: Store at room temperature: 15° to 30°C (59° to 86°F).
See crimp for lot number and expiration date.
Manufactured for: MEDICIS, The Dermatology Company Scottsdale, AZ 85258 by: Patheon, Inc. Mississauga, Ontario Canada L5N 7K9 Made in Canada U.S. Patent 6,765,001
Vanos
(fluocinonide)
cream 0.1%
FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE
Rx only
60 g
MEDICIS
UUDEX CREAM 0.05% 60g TUBE